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DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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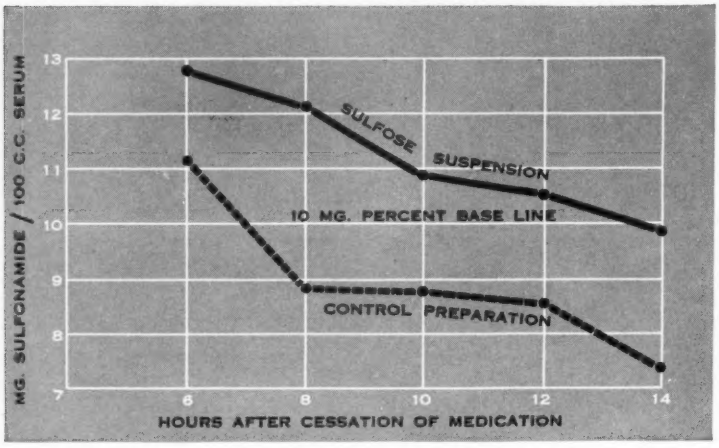

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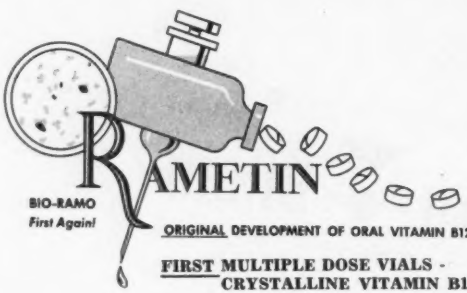

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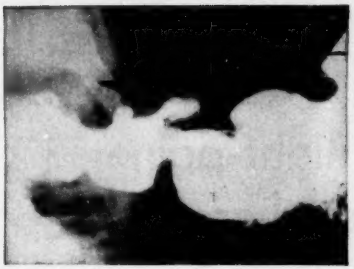

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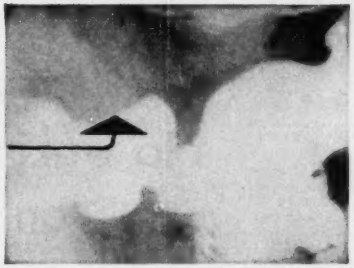

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*Offenkrantz, W. G.: Rev. Gastroenterol, *17*:359, 1950.

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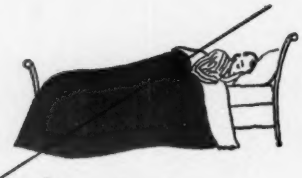

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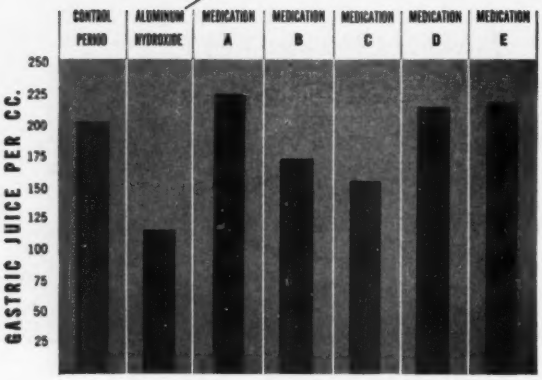

Average volume of gastric secretion from midnight to 5:30 A.M. in patients with duodenal ulcer treated with various medications *during the day* only. Aluminum hydroxide depresses volume of gastric secretion more effectively throughout entire night period. (Adapted from Brehaus, H. C., Akre, O. H., and Eyerly, J. B.: *Gastroenterology*, 16:172, Sept., 1950.)

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THE EFFECT OF ACTH IN A CASE OF BETA ISLET CELL ADENOMA OF THE PANCREAS

G. Malcolm Brown, M.D., D.Phil. (Oxon), F.R.C.P. (C), F.A.C.P., Kingston, Canada

SINCE THE WORK of Browne and his colleagues (1) and of Sayers and his colleagues (4), it has been known that exogenous adrenocorticotropic hormone will induce hyperglycaemia when given in a sufficiently large dose. The work of Conn, Lewis and Wheeler (2) showed that a temporary diabetes mellitus can be produced in normal adults by giving the hormone in large doses over a period of days. Recently McQuarrie et al. (3) have reported beneficial effects following the use of adrenocorticotropic hormone in a number of cases of spontaneous hypoglycemosis of the familial type. The present report records the results of the use of adrenocorticotropic hormone in a case of beta islet cell adenoma of the pancreas.

Case History

Case No. 10647-50. Female age 60 years. This woman began to suffer from periods of confusion and restlessness in May, 1950. Subsequently she was able to recall earlier minor episodes during the previous three months which were characterised by a feeling of faintness, giddiness, excessive perspiration and vague abdominal discomfort. After a period of observation in another hospital it was found that her fasting blood glucose varied from 14 to 52 mg. per cent and that her somnolence and confusion were relieved by the administration of glucose intravenously. During one of her hypoglycaemic episodes she suffered a right-sided hemiplegia. She was first admitted to the Kingston General Hospital on July 17, 1950, and investigation showed that a 24-hour fast resulted in irritability, restlessness and perspiration with blood glucose levels of 46, 42 and 39 mg. per cent during the last three hours of the fast. The symptoms were immediately relieved by the administration of glucose. Examination by barium meal showed no enlargement of the head of the pancreas. The serum amylase was 46 units (Somogyi). She showed general arteriosclerosis of moderate degree, a blood pressure of 240/120 and some weakness in the right hand. Otherwise the clinical examination was unremarkable.

On 2nd November 1950, 9.5 cm. of the tail of the pancreas was removed by Dr. D. L. C. Bingham. The resected portion contained a nodule 12 mm. in diameter which histologically was shown to be an islet cell adenoma. The post-operative course was uneventful and the patient is now well.

Kingston General Hospital and Queen's University, Kingston, Canada.

Effect of ACTH

On 10 October 1950 ACTH (Armour) administration was begun and for three days she received 25 mg. every six hours. Subsequently she received 10 mg. every six hours for three days and then 10 mg. every twelve hours for 10 days. The direct eosinophile count was 22 per cu. mm. both immediately before and four hours after the first injection of 25 mg. of ACTH. During the period of ACTH therapy there was no effect on the patient's blood pressure, which by this time had fallen to 150/90, and there was no weight gain. She was left on the high protein, high caloric diet with frequent feedings on which she had been for four months. The effect of the fasting blood sugar levels was disappointing (Fig. 1). While she was receiving ACTH 100 mg. a day there was a slight rise to a maximum of 70 mg. per cent but when the dosage was reduced to 40 mg. per day, it returned within two days to its old level. Blood sugar was determined by the method of Somogyi (6) on the deproteinised specimen prepared according to the method of Shaffer and Hartmann (5). For some weeks before the beginning of treatment she had experienced only mild hypoglycaemic symptoms on the occasional morning. During the period she was receiving ACTH 20 mg. per day these returned and five days following the termination of treatment she had major symptoms going on to stupor and a blood sugar of 39 mg. per cent.

The results of oral glucose tolerance tests carried out before the beginning of ACTH therapy and again on the last day she received 40 mg. of ACTH are shown in Fig. 2. On the day of the second test she received ACTH 10 mg. intramuscularly two hours before the fasting specimen was obtained and again at the end of the fourth hour of the test. It can be seen that except for the values at two hours, the points on the glucose-time curve obtained at the time of the second test are all somewhat higher than they were during the first test. Even so, the fasting blood sugar and the values at the fourth and fifth hours are all below 50 mg. per cent.

Discussion

The effect of ACTH was favourable in this case with a subsequently proven beta islet cell adenoma of the pancreas but the changes were not of sufficient degree to permit contemplation of long term management by this method of treatment even if the possibility of a malignant tumor had not influenced the decision. Though no untoward effects of the hormone therapy were seen during the relatively short time it was used, they were to be expected if therapy was con-

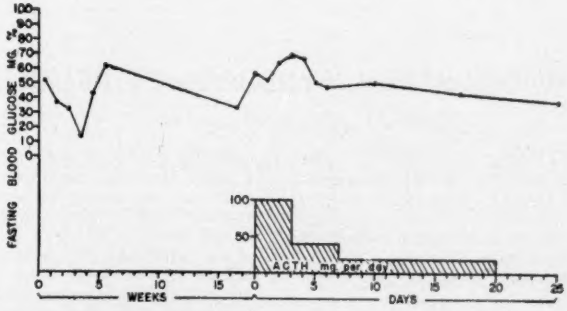

Figure 1. The effect of ACTH on the fasting blood sugar.

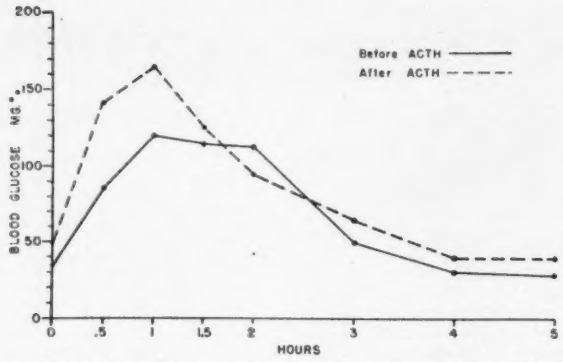

Figure 2. Oral glucose tolerance tests before and on the seventh day of ACTH therapy.

tinued in a dosage of 100 mg. per day, and it was only that dosage which had a significant effect on the fasting blood sugar. Two days after the dosage was reduced to 40 mg. per day the blood sugar had fallen to 50 mg. per cent and on the third day it was 45 mg. per cent.

This early fall in the blood sugar when the effective dose was slightly more than halved, differs from the experience of McQuarrie et al. in their cases of familial spontaneous hypoglycemosis. They found after the cessation of a four day period of treatment with 36 mg. of ACTH per day that marked hypoglycaemia was abolished for at least a week and that the fasting blood sugar remained, for this interval, at levels significantly higher than those observed in the pretreatment period. In their most severe case, an infant, it was possible to maintain the blood sugar at an asymptomatic level varying between 40 and 68 mg. per cent by carrying on after a period of intensive treatment with a single injection every 48 hours of 10 to 18 mg. of ACTH, approximately an eighth to a quarter of the first dosage. Their cases which have a patently different etiology from the present case, showed hypersensitivity to insulin. Tests with intravenous epinephrine and subsequent eosinophile counts gave results which suggested that the ability of the pituitary to release ACTH was normal. Sections from the pancreas in two of their cases showed a decreased number of alpha cells in the islets and this information temptingly leads to the hypothesis that these cells are perhaps the site of formation of an insulin-antagonist which circulates in deficient quantities in their cases. In the present case the cause of the hypoglycaemia is clearly an excessive secretion of insulin and the effect of ACTH, while favourable, was not as dramatic as in McQuarrie's cases where the cause of the hypoglycaemia is probably a deficiency of insulin antagonists. The effect, in fact, was not great enough to indicate that ACTH therapy over a period of time in such cases is a practical method of management.

The ACTH used in this case was supplied by the National Research Council, Canada.

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THE GASTROINTESTINAL SYNDROME OF REDUCIBLE HERNIA

HARRY GAUSS, M.D., Denver, Colorado

A GASTROINTESTINAL SYNDROME frequently occurs in reducible hernia. Sometimes the digestive symptoms simulate peptic ulcer or other forms of the gastric irritation syndrome, sometimes they simulate the irritable colon syndrome, sometimes variants or combinations of these.

To the patient, the digestive syndrome often dominates the clinical picture, while the hernia may occupy a place of minor importance. Actually the gastrointestinal syndrome is reflex in origin, functional in character and of secondary importance; but it may occupy the place of major importance in the opinion of the patient, who is greatly concerned with what he believes to be a peptic ulcer, or some other digestive disturbance. Because of this, the symptom complex as presented by the patient often requires careful analysis to determine the causal relationship of the

Department of Medicine, University of Colorado, Denver, Colorado.

hernia and digestive syndromes with reference to the etiologic and pathogenetic relationships.

The patient is often primarily concerned with what he believes to be a peptic ulcer or some other digestive disturbance from which he seeks relief, while the rupture with which he is also familiar is a matter which he believes can wait for treatment at some future convenient time.

Actually it is the hernia which is the primary cause of the patient's symptoms, and it is this which initiates the reflex digestive syndrome, hence it is the hernia which requires primary therapeutic attention. The digestive syndrome will usually subside spontaneously following the correction of the hernia.

Case Report. A typical case report illustrating the occurrence of the reflex digestive syndrome occurred in patient J.E.G., a young man, age 30, who came to the office complaining of heartburn and distress in the pit of the stomach three months in duration, which was somewhat relieved by the taking of soda. The patient had been reading some medical articles on peptic ulcer, also he had been exchanging gossip with other members of his traveling salesmen friends, several of whom had true duodenal ulcers; so he thought that he had a stomach ulcer. Because of this belief, he had gone on a self imposed ulcer diet with a regime of antacids borrowed from one of his friends. However, he did not experience the complete relief described by the possessors of true ulcers and so he came to the office seeking a more potent remedy than that which he was already taking.

His general health was otherwise good. His habits were moderate. He possessed a high tension personality which is common to many of his calling. Throughout the entire history, not a word was mentioned of the existence of an inguinal hernia.

Physical examination showed a white male, 30 years old, not acutely ill. He was 5 feet, 10 inches in height. His pulse was 84, his temperature was 98.8, his respiration was 16; his blood pressure was 130/68. The eyes reacted to light and accommodation. There was no ptosis and no strabismus. The throat was clear, the tonsils were out. The heart borders were normal, the tones were clear, there were no murmurs. The lungs had good resonance; there were no rales and no

GASTROINTESTINAL SYMPTOMS OCCURRING IN REDUCIBLE HERNIA

No. Case	*Age*	*Sex*	*Duration*	*Gastrointestinal Symptoms*	*Type Hernia*	*Treatment*	*Effect on Gastrointestinal Symptoms*
1. JEG	30	M	3 months	Heartburn, relief by soda, epigastric distress	Left Inguinal	Herniotomy	Complete Remission
2. MRI	60	M	5 years	Bloating, distention, constipation, diffuse abdominal pain, nausea, vomiting	Ventral	Surgery Refused	Symptoms Persisted
3. BES	52	M	2 years	Epigastric distress, fullness after meals, flatulence, constipation	Left Inguinal	Herniotomy	Complete Remission
4. CW	51	M	1 year	Distress right costal margin, bloating, fullness after meals, constipation, nausea, occasional vomiting	Bilateral Inguinal	Bilateral Herniotomy	Complete Remission
5. BM	35	M	1 year	Epigastric distress, heartburn, bloating	Left Inguinal	Herniotomy	Complete Remission
6. BTB	42	M	2 years	Distress costal margins, nausea, bloating, constipation	Left Inguinal	Herniotomy	Complete Remission
7. JW	26	M	6 months	Epigastric distress, heartburn, relief by soda, upper abdominal distress	Right Inguinal	Herniotomy	Complete Remission
8. ACD	35	F	1 year	Constipation, lower abdominal distress, fullness after meals, coated tongue, headache	Left Femoral	Herniotomy	Complete Remission
9. HJP	41	M	4 years	Epigastric distress, heartburn, relief by soda, dizziness, headache	Left Inguinal	Herniotomy	Complete Remission
10. WMS	60	M	6 years	Nausea, vomiting, bloating, constipation, diffuse abdominal distress	Left Inguinal	Herniotomy	Complete Remission
11. RB	45	F	2 years	Costal margin distress, nausea, vomiting, bloating, constipation	Left Femoral	Herniotomy	Complete Remission
12. RRB	40	M	1 year	Diffuse abdominal distress, constipation, flatulence, bloating	Left Inguinal	Herniotomy	Complete Remission
13. DHB	25	M	6 months	Epigastric distress, heartburn, fullness after meals, upper abdominal distress	Right Inguinal	Herniotomy	Complete Remission
14. RIS	36	M	2 years	Epigastric distress, heartburn, relief by food, upper abdominal distress	Left Inguinal	Herniotomy	Complete Remission
15. BSB	40	M	3 years	Belching, bloating, constipation, headache, fatigue	Left Inguinal	Herniotomy	Complete Remission
16. JA	28	M	3 months	Diffuse abdominal distress, bloating, nausea, cramps, distress left lower quadrant	Left Inguinal	Surgery Refused	Symptoms Persisted
17. LS	32	M	1 year	Upper abdominal distress, heartburn, fullness in epigastrium, belching	Left Inguinal	Herniotomy	Complete Remission
18. MRT	48	M	2 years	Constipation, headache, nausea, fullness after meals, costal margin distress	Left Inguinal	Herniotomy	Complete Remission
19. LSK	55	M	5 years	Constipation, diffuse abdominal distress, belching, bloating, fullness after meals	Left Inguinal	Herniotomy	Complete Remission
20. STS	40	M	3 years	Upper abdominal distress, fullness after meals, costal margin distress, headaches, constipation	Left Inguinal	Herniotomy	Complete Remission

rubs. Chest expansion was good. The liver and spleen were not palpable. There were no scars and no tumor masses present. The left external abdominal ring was enlarged and a distinct impulse could be detected on coughing with a downward plunge of the hernial contents which entered the inguinal canal. The right external ring was normal. There were no hemorrhoids, and the reflexes were present and equal.

The urine analysis was normal, the blood count was within normal limits; the Ewald test meal at one hour gave a free acid of 28 and a total acidity of 55, blood was not present. The basal metabolic rate and the electrocardiogram were within normal limits.

X-ray of the stomach and duodenum showed these to be free of filling defects. The cap was somewhat irritable but nevertheless filled well. The stomach emptied normally within six hours. The small intestine was normal in configuration and the colon was spastic and irritable.

Diagnosis. Left Inguinal Hernia, Secondary Digestive Syndrome.

Treatment. The nature of the digestive symptoms was explained to the patient as being reflex in origin and coming from the hernia, which was the primary problem. A herniotomy was advised and performed. The patient made an uneventful recovery, and the digestive symptoms subsided spontaneously following the herniotomy. The patient returned a year later to report progress. He stated that he felt fine, there was no recurrence of his rupture and likewise he was free of digestive symptoms.

We have selected twenty case reports from our files in which the patients complained primarily of a digestive complaint, in whom was found a hernia which was considered by the patient to be of minor importance. In eighteen of these patients a corrective herniotomy was performed, and in these there occurred a spontaneous remission of the digestive symptoms. The other two patients refused surgery; so they remain as controls to illustrate that the digestive symptoms persisted in spite of symptomatic medical treatment.

Analysis of the symptoms of the twenty patients shows that the digestive symptoms fall into three groups: (1) the gastric irritation syndrome, which may at times simulate the peptic ulcer syndrome, (2) the irritable colon syndrome, and (3) variants of these.

DISCUSSION

In this discussion, we have included only the early acquired hernia in the reducible stage, since the irreducible and the strangulated types give pronounced local symptoms which directs the attention to the primary problem. Likewise instances of diaphragmatic hernia have been omitted since the symptom complex that it gives rise to, aided by the x-rays, directs immediate attention to the primary problem.

It is generally accepted that the contents of the hernial sac are (1) omentum, (2) small intestine and (3) large intestine.

Now it is obvious that long before incarceration takes place, that irritation of the contents occurs even in the reducible stage of hernia, and that there are many more instances of irritation of the hernial contents than incarceration. In fact, irritation of the hernial contents is apt to be a common occurrence. Even the wearing of a truss does not prevent such an irritation, as we have observed many instances of badly fitting appliances, causing us to wonder at times whether they were helpful to the patient or whether they only added to his problem.

In seeking for an explanation for the gastrointestinal syndromes which occur, we recall that in the mechanism of hernia formation, that a protrusion of the parietal peritoneum takes place in some weakened portion of the abdominal wall forming an adventitious sac into which enters some abdominal viscera. The contents of these sacs in the order of their frequency, according to Watson, are: the omentum, the ileum, the jejunum, the sigmoid, the caecum, the appendix, the pelvic organs, and other viscera.

Irritation of the ileum could easily give rise to upper abdominal or epigastric pain which might simulate a peptic ulcer; whereas irritation of the colon would give rise to the irritable colon syndrome.

Watson states that the first stage of inguinal hernia may often be characterized by an uneasiness in the epigastrium without actual pain, and often a dragging sensation in the costal margins, and sometimes a referred pain in the back in the region of the ninth and tenth ribs.

The gastric irritation syndrome as seen in eight of our patients consisted of heartburn, distress in the epigastrium which was diffuse in its distribution, however it was somewhat relieved by the taking of food or alkalies. It sometimes occurred at the end of the gastric cycle, at times unrelated to the taking of food. This type of the gastric irritation is apt to simulate peptic ulcer. At other times there is a fullness in the epigastrium after meals associated with belching, bloating or nausea and occasional episodes of vomiting. X-ray of the stomach will exclude a peptic ulcer by showing a gastric outline free of persistent defects; although the duodenal cap may be somewhat irritable. However it can be observed to fill well under fluoroscopic examination.

The irritable colon syndrome observed in nine patients in our series complained of diffuse abdominal pain or uneasiness which appeared at irregular times during the day. Sometimes the distress was localized in either or both costal margins. Sometimes there was nothing more than an abdominal consciousness with excess flatulence and belching. Constipation with small constricted stools are the rule. The stools are infrequent and unsatisfactory to the patient. Dull headaches and coated tongue are apt to accompany the constipation. Loss of appetite may occur. X-ray studies usually show an irritable colon with some spasticity, hypertonicity and irritability. The colon has a reduced lumen and often assumes a stringy appearance. These changes are purely functional in character, because after a sedative to the patient the colon will usually resume its normal appearance.

Some patients will exhibit a mixed syndrome which suggests an overlapping of these syndromes.

The symptoms are at times vague and evanescent and will subside with sedatives and rest. They are functional in character and are dependent for their continuance upon irritation applied to the hernia contents.

That some lesions in the lower part of the abdomen or even within the pelvis can give rise to distress in the upper part of the abdomen or elsewhere is a clinical phenomenon that has received some attention in the literature; however, referred symptoms of reducible hernia origin have not received the attention that the subject merits. Watson mentions the occurrence of epigastric pain and a dragging sensation in the costal

margins occurring in reducible hernia. Coley mentions that strangulated femoral hernia may be mistaken for other abdominal conditions.

Elsewhere we have discussed the occurrence of upper abdominal pain in anorectal disease, mentioning that the referred symptoms may be manifested in the epigastrium, upper abdominal region, the hypochondria, or the entire abdomen. Such symptoms may take on a gastric or gastrointestinal character producing at times an ulcer-like syndrome. Likewise there occurred an irritable colon syndrome. The mechanism of the production of the reflex gastrointestinal symptoms originating in the anorectal region is generally regarded as taking place through the medium of the sympathetic and parasympathetic nervous systems. Anything which is capable of initiating an irritation, either within the lumen or on the wall of the gut, is also capable of initiating a contraction of the bowel which may involve an extensive segment, and so refer its symptoms to a remote portion of the abdomen. Normal activity of the gastrointestinal tract is maintained by an interplay of the impulses from the sympathetic and parasympathetic nerves (the vagus and pelvic nerves). An irritation originating in the anorectal region, acting through the sympathetic nerves, is capable of causing an irritation of the gastrointestinal tract and so producing a gastric or colon syndrome.

Likewise we have discussed the production of digestive symptoms by disturbances originating within the pelvis, mentioning that the significant factor in the initiation of the abdominal distress of pelvic origin is the pressure of the pelvic viscera on the contiguous bowel or a spread of the inflammatory process from the pelvic to the digestive viscera. However, in the case of pelvic causes, there are also present certain factors which do not operate in the case of referred symptoms of hernial origin. These special factors are pregnancy and the endocrines.

Quite likely the referred symptoms originating in the reducible hernia operate in much the same manner as in referred rectal distress, namely, through the medium of impulses transmitted through the sympathetic nerves. Irritation of the contents of the hernial sac initiates an irritation of the bowel, which can refer its symptoms to remote portions of the abdomen.

The abdomen has been called the spokesman of the body. However, it tells of trouble, but it does not locate it. That task remains for the physician, who must determine the primary problem existing in the patient. This is done upon careful consideration of the history and physical examination, aided by the laboratory and x-ray studies of the patient.

TREATMENT

The treatment of the digestive syndrome occurring in reducible hernia is obviously to remove the cause, and since the primary cause is the hernia itself, the surgical correction of the hernia is indicated. Therefore, unless a definite contraindication exists, a herniotomy should be performed. In all of the patients whom we have observed, the surgical correction of the hernia was followed by a spontaneous remission of the digestive symptoms. In two patients where surgery was refused, the digestive symptoms persisted in spite of medical management.

Hernia and primary disturbances of the digestive tract can, of course, coexist. Thus it is possible for a person to have an inguinal hernia and a peptic ulcer or gall stones at the same time. Primary gastrointestinal disease, if present, should be given proper treatment. This study, however, is concerned with that group of patients in whom the digestive symptoms are reflex in origin and functional in character, and originate in the reducible hernia. In this group of patients, the surgical correction of the hernia is followed by a spontaneous remission of the digestive symptoms.

SUMMARY

1. Reducible hernia may give rise to a gastrointestinal syndrome.

2. The digestive syndrome may simulate peptic ulcer, the gastric irritation syndrome, the irritable colon syndrome or variants of these.

3. The patient frequently considers the digestive symptoms his primary problem.

4. The gastrointestinal syndrome is reflex in origin and functional in character.

5. The referred symptoms are mediated through the sympathetic nerves. Irritation of the contents of the hernial sac initiates an irritation of the bowel, which can refer its symptoms to remote parts of the abdomen.

6. Treatment of the referred gastrointestinal syndrome consists in correcting the hernia surgically; following which the digestive symptoms usually subside spontaneously.

7. Patients may have coexisting hernia and primary digestive problems. When the digestive problems are present, they require appropriate treatment.

8. The abdomen has been called the spokesman of the body. It tells of trouble, but it does not locate it. The task of locating the source of the symptoms is the responsibility of the physician.

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THE "BOLEN TEST" IN THE DIAGNOSIS OF NEOPLASMS

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THE DIAGNOSIS OF CANCER, or its exclusion in the diagnosis, is very important in the practice of medicine. The Bolen Test, using freshly dried blood smears, was recently described by Norman and Slicher (1) and is one of the latest aids in such diagnoses. This test is simple, can be reported in a short time, and is very inexpensive. We were impressed with the results they reported and have tried to reproduce them.

Their technic was followed as closely as possible. In order to eliminate all possible sources of error, at least one slide was made on all patients by the same technician. Patients were taken routinely as they presented themselves for examination. The ages ranged from 16 to 83 years. Neither sex, previous pregnancies, or number of children borne had any noticeable effect on the results. Likewise, the results were not influenced by the following uncomplicated conditions: congenital anomalies, moderate hypertension, obesity, cholelithiasis, asthenias, moderate secondary anemias, chronic peptic ulcers, diabetes mellitus and cardiac conditions. Also the usual benign conditions found in the aging, with the exception of marked arteriosclerosis, did not seem to influence the result.

On the other hand, we found some non-malignant conditions, as did Norman and Slicher, that did give positive tests in a large per cent of the cases. Such conditions were pregnancy, active tuberculosis, diseases of the female reproductive system, and active thyroid conditions. Frequently where the serum bilirubin was two or more, we obtained a positive result. We also found many positive results in active inflammatory processes such as tonsillitis, breast mazoplasia, pyuria, Bartholin gland abscess and diverticulitis.

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In 80 consecutive cases with no malignancy, the Bolen Test was negative in 53 cases (66 per cent) and positive in 27 cases (34 per cent). Most of these positive results occurred in conditions that Norman and Slicher also reported positive results. However, we did have a positive result in six cases where we did not expect a positive result. These six cases consisted of two cases of only moderate secondary anemia, two cases of myocardial degeneration with early decompensation, an arthritis which apparently was quiescent and a hypertensive case with associated lower nephron nephrosis. No attempt was made to classify the patterns in the non-malignant cases. Our results seemed to parallel these previously reported. We did note that the non-malignant positive cases usually did not produce the large "lakes" in the pattern produced by the malignant conditions.

Since the "modus operandi" of this test is not known definitely, we thought that the conditions under which the smears were dried might affect the result. However, slides dried in ordinary air and in a covered petri dish were comparable. Slides dried in the refrigerator took longer to dry and seemed less clear cut. Slides exposed to drafts or direct sunshine were distorted and harder to evaluate. All attempts to preserve slides with fixation

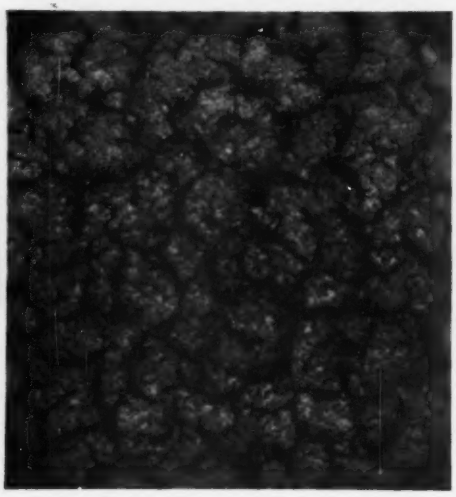

Fig. 1 — Male, 66 years. Old duodenal ulcer deformity, nephrolithiasis, sedimentation rate 12, symptomless. Normal clot retraction.

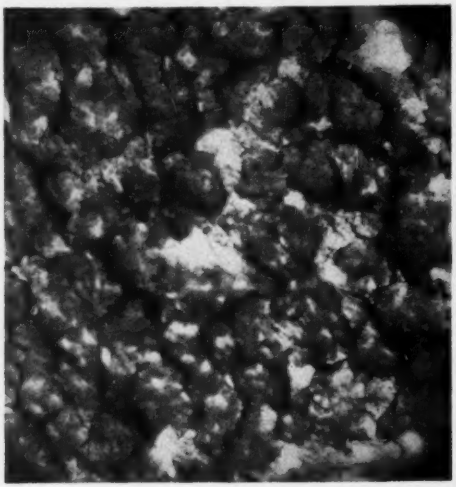

Fig. 2 — Male, 45 years. Benign adenomatous rectal polyp, sedimentation rate 31. Slight disturbance of clot retraction.

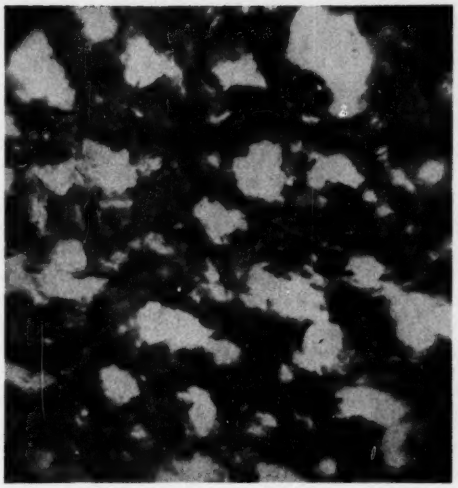

Fig. 3 — Male, 55 years. Cancer of prostate grade 3.

or coating were unsuccessful due to distortion of the pattern. More work along this line will probably devise a standard procedure.

The illustrations show the normal configuration and some variations.

Our most interesting and important finding in these tests was a very low incidence of false negative results. We had 48 patients with a recognizable neoplasm and at least three slides of blood smears were made on each patient. In only two out of all these slides was the Bolen Test first read as negative or doubtful and in both instances another slide was found to be definitely positive. This raised the possibility of using the Bolen Test as a screening test for the exclusion of cancer, similar to the use of the Mazzini and Kline screening tests for syphilis.

Since the public has become more cancer conscious, more patients are seeing their local doctors with greater frequency. There are many patients of both sexes who have a fear of cancer. This is especially true in cases of peptic ulcer, neurasthenias, the menopausal syndrome, indefinite abdominal complaints and in patients whose relatives had a neoplasm. If such an elimination test would be reliable, we felt it could be used extensively to preclude the presence of a neoplasm. Therefore, we did a routine Bolen Test on such patients in whom we had no definite reason to suspect a neoplasm. Up to the present time, in 110 cases, the Bolen Test has been reliable. Also in some of these patients with a negative Bolen Test, with subsequent surgery, no malignancy was found. Consequently, if such tests continue to be correct in a large series, they will be a very valuable aid in medical diagnosis.

CONCLUSION

We were able to corroborate many of the findings reported by Norman and Slicher. When the Bolen Test is positive repeatedly, especially with large "lake areas," a malignancy should be looked for diligently. When the Bolen Test is definitely negative, especially on more than one occasion, it is very good evidence (in our limited series) that no recognizable neoplasm is present at that time.

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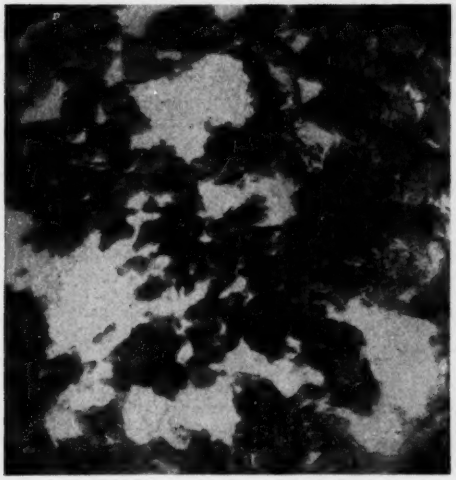

Fig. 4 — Female, 49 years. Cancer of cervix with metastases.

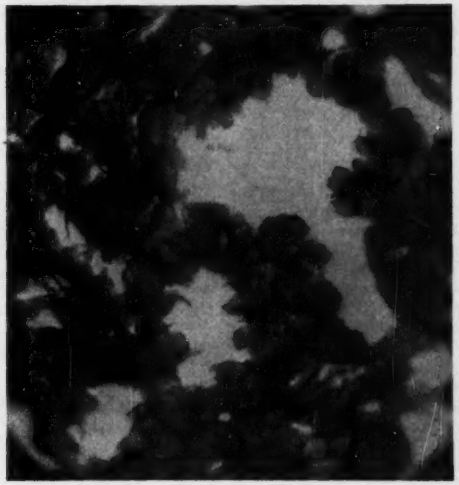

Fig. 5 — Female, 53 years. Cancer of cervix.

MODERN CONCEPTS IN THE TREATMENT OF FISTULA IN ANO

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THE TREATMENT OF FISTULA IN ANO is often poorly understood; and, judging from the number of cases operated on several or more times without success, it would seem that the treatment leaves much to be desired. The accepted modern principles of rectal surgery have not been too well applied to the surgical treatment of fistulas. Time only permits a brief discussion of the details in the preparation of the patient, operative techniques, and post-operative fistula care; however, an attempt will be made to emphasize some of the pitfalls in fistula treatment, and additionally to evaluate the use of our newly acquired chemo-biological aids. I use the word "aids" advisably since the "miracle" drugs are not and should not be considered as substitutes for sound, well proven surgical principles such as adequate drainage, removal of diseased tissue, and the rapid restoration of normal function.

DIAGNOSIS

A careful history and skillful ano-rectal examination (including a procto-sigmoidoscopic examination) should be made in every case before arriving at a diagnosis. Coexisting lesions such as idiopathic ulcerative colitis, ano rectal abscess, malignancies, familial polyposis, intestinal tuberculosis, regional ileitis, amebiasis, lymphopathia venereum, granuloma inguinale, rectal stricture, diverticulitis, actinomycosis, primary syphilis, and gonorrhea are all contra-indications for fistula surgery. Other conditions requiring temporary postponement of surgery are pregnancy, acute inflammatory lesions, adenomas, prostatitis, or bleeding peptic ulcers. The importance of an accurate preoperative diagnosis in all cases may be dramatically illustrated by a recent study of colloid adenocarcinomas involving the perianal region. Hill and Smith (2) have reported seven colloid adenocarcinomas which clinically resembled anal fistulas. Binkley (3) found mistaken diagnosis and erroneous forms of treatment in 32 cases of epidermoid carcinoma of the anus and rectum. Cancer of this part of the body can easily be detected. All suspicious looking lesions should be biopsied.

PRINCIPLES OF FISTULA TREATMENT

It is unwise to operate upon a fistula when an acute inflammation or undrained abscess is present (4). Anal abscesses are usually the first stage of a fistula, and must be diagnosed as early as possible so that adequate drainage may be started. I have a strong feeling that delay in adequate drainage is responsible for the extensive destruction of tissue and formation of complicated fistulous tracts.

In the treatment of residual fistula, the primary or internal opening should be located before surgery is begun. Since most fistulas arise in a crypt, anal duct, or anal gland, the author always removes the entire crypt together with the mucosa slightly above the effected anorectal or dentate margin. Any questionable areas are thoroughly curetted. In this way the primary infectious focus is thoroughly uncapped and exposed. The primary openings of fistulas will be found posteriorly slightly to the right or left of the midline in at least eighty per cent of the cases (5). To recognize the remaining twenty per cent requires considerable skill and manipulation. Fistulectomies are successful only if all the infected tracts, including all side tracts, are properly incised or excised and all overhanging edges of tissue are trimmed away, leaving a clean, raw, saucerized wound, where the abscess was or where the fistula tracts were eradicated. In the case of tuberculous fistulas, complete fistulectomy with thorough excision of all the diseased tracts and tissue is usually necessary for a cure.

There should be little need for packing, and certainly no packs should be left in situ more than 48 hours. A very careful search should be made to discover a deep cross tract through the posterior communicating space behind the anal canal. (6)

A thorough knowledge of anatomy is essential for the successful cure of fistulas, since confusion regarding anatomy of the anorectal musculature with a resulting lack of ability to recognize important anorectal landmarks may give the operator a sense of insecurity which, when coupled with a fear of incontinence, often results in incomplete division of the main tract through the deep sphincter muscles, with a resulting recurrence of the fistula. When in doubt as to how much of the sphincter muscle may be divided without loss of control, it is always advisable to place a wire seton around the musculature of the undivided tract. The seton should be cut out when the wound is healed sufficiently to prevent a deforming retraction of the divided sphincter muscle fibers, which usually is about two weeks (7). Injection of fistulas with a suitable opaque media and proper stereoscopic technique in the use of x-ray will usually demonstrate the extent of the pathology present.

PREOPERATIVE PREPARATION

Preoperative preparation should include thorough emptying of the bowel with castor oil or saline catharsis such as phospho-soda followed by a thorough cleansing with a physiological saline enema repeated until returning clear. Preoperative use of antibiotics will be discussed presently.

ANESTHESIA

There are many methods of anesthesia depending on the wishes of the patient, the surgeon, and the skill of the anesthetist. The author prefers the following method: preoperative medication of morphine and scopolamine in small doses is given one hour before the operation. The patient is arranged on the operating table in the most advantageous position (usually lithotomy). Sodium Pentothol is started immediately, after which the patient is carried with Sodium Pentothol and Cyclopropane, which gives adequate relaxation for the average fistula case. The postoperative

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recovery is extremely good, induction pleasant, and the patients are happy with the way they react. When more complete relaxation of the musculature is necessary, spinal anesthesia is still the anesthesia of choice.

SULFA AND ANTIBIOTIC THERAPY

It is not routinely advisable to use sulfa and antibiotic therapy in all cases of rectal fistula. Experience and good judgment are the best guides for the selection of the most desirable therapy for the case in question. There is a developing tendency among physicians to disregard the significance of possible toxic reactions and to administer antibiotics or sulfonamides to patients who are suffering from diseases in which it is improbable that the drug will be effective. Too little thought is being given to the fact that such practices may sensitize the patients to these drugs with the result that the future use of a valuable, perhaps life saving remedy will be seriously compromised. There can be little questioning the fact that the topical route for the administration of sulfonamides or antibiotics is most conducive to establishing a state of sensitization in the patient (9).

When indicated, a slowly absorbed sulfa drug such as Phthalylsulphathiazole (sulfathalidine) should be administered, starting three to five days preoperatively and continued until wound healing is well established. Phthalylsulphathiazole produces a smooth, semi-formed stool and tends to decrease the infection in the wound, thus lessening afterpain and encouraging healing with a minimum amount of scar tissue (10). Succinylsulfathiazole (Sulfasuxidine) is equally as effective as Phthalylsulphathiazole but tends to produce loose stools which may be irritating. Sulfathiazole and combinations of sulfa drugs containing sulfathiazole are to be avoided because of their tendency to produce toxic reactions; it is for this reason that the Council on Pharmacy and Chemistry of the American Medical Association has deleted sulfathiazole from New and Nonofficial Remedies (11). Sulfamethazine has been found to be a very satisfactory substitute for sulfathiazole. In cases showing systemic manifestations or infection, the writer has found tablets of triple sulfonamides containing Sulfamerazine 0.1 Gm., Sulfadiazine 0.2 Gm., and Sulfamerazine 0.2 Gm. very effective with almost negligible toxic effect.

ANTIBIOTICS

The antibiotics should be used under laboratory control in the abscess stage of fistula or fistulas with secondary abscess and widespread infection. Cultures should be taken before the injection of the antibiotics, and the sensitivity of the prevailing bacteria to penicillin, bacitracin, streptomycin, or other antibiotics determined. Since penicillin has the broadest bactericidal spectrum it should be used at the time the culture is taken and continued until the culture is reported. If clinical response is not prompt and favorable, the culture and sensitivity findings are a guide to further antibiotic therapy; or in the case of anaerobes, to the use of sera.

Crystacillin in dosage of 300,000 to 600,000 units daily is very effective with a minimum of toxic reaction.

Bacitracin is effective against gram positive cocci infections and nonhemolytic streptococci as well as other bacteria which are resistant to penicillin and sulfa drugs. It is not locally toxic or irritating and is not inhibited by discharges containing plasma, blood, pus, broken down tissue, or organisms which produce penicillinase. In strictly localized infections, bacitracin may obviate the need for incision and drainage formerly used. Bacitracin may be used in strengths of 500 units per cc., locally or for infiltration. It should not be used parenterally until further purified to eliminate the nephrotoxic factor. It may be useful to note that the systemic injection of penicillin simultaneously with the local infiltration of bacitracin covers a wide spectra of organisms commonly involving the perianal tissues. This is an indicated procedure where culture control is not available or is neglected, as is commonly the case.

Streptomycin is effective against gram negative bacilli exerting a profound antibacterial effect on the intestinal flora. It is also effective against some gram positive bacteria, and is not destroyed by gastric juices. Administered orally, streptomycin can be expected to reduce bacterial count and the virulence of the bacteria of the entire intestinal flora including colon bacillus, streptococcus fecalis, anaerobes of the Welchii group, salmonella, and the shigella paradysenteriae. A combination of sulfathalidine and streptomycin is one of the most effective antibacterial procedures for preoperative preparation; it should be administered by mouth. For the treatment of tubercular fistulas, the parenteral administration of dihydrostreptomycin is to be preferred.

To avoid organisms becoming streptomycin fast, it is advisable to give maximum dosage at the start of therapy. Serious toxic symptoms may develop following prolonged treatment with streptomycin.

Aureomycin and chloromycetin have irritating qualities when injected locally; however, they are of great adjunctive value in the anorectal infections and fistulas complicating the proctocolitides, particularly chronic ulcerative colitis, amebiasis, and lymphopathia venereum. It is essential to recognize that the healing of local anorectal lesions is directly related to the progress effected in the primary colonic or rectal disease.

Chloromycetin is preferred in the typhoid, paratyphoid, and dysenteric infections; Aureomycin, in the amebic and lymphopathic group (12). Both drugs are preferably given by mouth in one gram divided daily doses at approximately four hour intervals. Caution should be used when administering aureomycin to a patient with a known duodenal ulcer. Two cases have been reported in which duodenal ulcers have perforated after they have received aureomycin (13).

Tyrothricin solution in the strength of 0.05 mg. per cc. is valuable for topical application and for irrigating infected areas. When used locally in this strength for short periods of time, we have not noticed any toxic manifestations. Its activity is limited to use against gram positive organisms.

New hope and enthusiasm are aroused whenever a new antibiotic is described. Neomycin is reported to be only about one-tenth as toxic as streptomycin but it is about five times more active. Wacksman, the discoverer of this antibiotic, found it to inhibit the growth of tubercle bacilli, salmonellae, brucellae, cholera, vibrios, and endamoeba histolytica in vitro and

in vivo. He has stated that organisms do not develop neomycin resistance.

The status of polymyxin, or aerosporin, as it is called by the British authors, is still confused. There appear to be at least four forms, one form, Polymyxin D, is active against gram negative organisms. It has little toxicity.

Enniatine, which was discovered in Switzerland, is a promising agent against acid fast organisms but is irritating in its present form.

Terramycin is a new actinomycete with a promising future due to its apparently low toxicity plus wide variety of micro-organisms (both gram positive and gram negative, aerobic and anaerobic) that are terramycin sensitive. This newer antibiotic may be especially valuable to the proctologist if the present claims become verified by the large group of clinicians and researchers now doing investigational work. Their studies suggest that terramycin may be of some value in many cases of lymphogranuloma venereum, granuloma inguinale, hemolytic and non hemolytic streptococci including streptococcus fecalis, staphylococcal aureus and albus, E. Coli, and endamoeba histolytica. Suggested dosages vary from one to five grams daily in divided doses given orally.

In prescribing antibiotics it should always be remembered that the modes of action of the various antibiotics is different. When confronted with a case of rapidly spreading virulent infection, superior results will be obtained by using a combination of several of the antibiotics. For example, it is good therapy,to use a combination of the first and second choice antibiotics in any severe infection, with the possible addition of the indicated sulfa drug (14).

Skin Grafts

In the treatment of extensive fistulas with the resulting large areas of granulation, skin grafting has been very successful (15). Split thickness grafts are used as soon as a clean flat granulating surface has been obtained. The grafts are fixed in place by saturating the donor skin with human plasma and flooding the recipient bed with a solution of Thrombin, Topical. This method has the beneficial effects of prompt hemostasis and the precipitated fibrin acts as a physiologic glue to hold the grafts in place. No dressings or sutures are used: During the first few days following grafting, a cradle is placed over the patients to protect the grafted area. The grafts are kept moist with a drip of physiological salt solution containing penicillin, 100 units per cc. of saline.

Vitamins

For more extensive complicated cases of fistula, the patient should receive preoperatively and postoperatively adequate dosages of vitamins parenterally and by mouth. Vitamins to be included are: the B complex (Betalin), two to four cc. intramuscularly daily, and Ascorbic Acid. Ascorbic Acid is given in dosages up to one gram per day.

Postoperative Care

Successful postoperative care is based primarily on cleanliness. There is no substitute for soap and water to cleanse the postoperative wound. Following routine Sitz Baths, patients are instructed to wash their perianal region thoroughly with pure Castile soap and water, using pledgets of cotton; and to thoroughly spray or shower off all the remaining soap with a portable hand spray which is attached to the bath tub faucet. The latter procedure, requiring five to ten minutes time, has done more to shorten healing time and give comfort to our patients than any single one of the "miracle drugs."

In the postoperative care, frequent routine digital examinations are necessary to insure satisfactory healing. These examinations are started about the fifth post-operative day. It is advisable to precede all routine examinations with the application of a topical anesthesia, Pontocaine, two per cent, or Topigesine (16) have been found very satisfactory for this purpose. Topigesine's lubricating and anesthetic properties aid in the painless passage of a probe, while its germicidal action will occasionally sterilize the tract. Bridging or pocketing in the wound must be removed.

Conclusions

1. Accurate diagnosis must always precede any attempt at curative treatment of fistulas, being sure to eliminate neoplastic disease.

2. A review of some of the more common reasons for failure of surgery in the cure of fistulas is discussed.

3. Sulfa or Antibiotic therapy should be used only as an aid to treatment and an adjunct to competent surgical management of fistula in ano.

4. An improved technique for skin grafting perianal wounds is outlined, using Thrombin, Topical to hold grafts in place, penicillin is added to the saline solution as a suitable bacteriostatic agent, with which to keep the grafts moist.

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STREPTOCOCCI, DIPLOSTREPTOCOCCI AND RESPECTIVE FILTRABLE AGENTS FROM OUTDOOR AIR DURING EPIDEMICS OF RESPIRATORY INFECTIONS AND INFECTIOUS GASTROENTERITIS

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THE IMPORTANCE of contact infection in the causation of localized epidemics is well established, but the underlying reasons for the seasonal occurrence, in temperate climates, of respective epidemics involving the respiratory and gastro-intestinal tracts of human beings almost simultaneously over vast and often isolated regions is still obscure.

Respective specific types of nonhemolytic streptococci have been isolated by special methods in studies of epidemic influenza, milder respiratory infections, encephalitis, poliomyelitis and from indoor and outdoor air and diplostreptococci in infectious gastroenteritis during respective epidemics (1, 2, 3). Filtrable infectious agents resembling the respective viruses of these diseases have been produced respectively from "pneumotropic" and "neurotropic" streptococci (4, 5, 6) and from "enterotropic" diplostreptococci (3).

The importance of nonhemolytic streptococci in one disease — primary or atypical pneumonia — currently considered as being due to a virus, has been reported, indicating that the streptococcus and the virus may be related (7). Moreover, the consistent occurrence of an erythematous cutaneous reaction following intradermal injection of thermal antibody prepared from nonhemolytic streptococci and from diplostreptococci isolated in studies of atypical pneumonia, influenza and other respiratory infections and infectious gastroenteritis respectively indicating specific antigen in skin or blood and hence a corresponding streptococcal or diplostreptococcal infection further indicate the importance of such organisms in the etiology of these diseases (8, 9).

An attempt was therefore made to isolate not only the respective streptococci and diplostreptococci from outdoor air but also filtrable infective agents or viruses associated with and which are currently considered as the cause of these diseases. It is the purpose of this paper to describe the methods used and report the results obtained in this further study made during epidemics of influenza and milder respiratory infections and of infectious gastroenteritis during the winter and spring of 1948 and 1949.

METHODS OF STUDY

Samplings of outdoor air were made by exposing chemically inert materials affording a large absorbent surface, such as variable-sized pebbles, loosely packed glasswool or fiberglas in glass tubes, 1½x12 cm. in bundles of seven, or in two light-weight metal tubes, 3½x20 cm. with screened open ends, to currents of outdoor air. Improvised weathervanes atop 12 foot poles at ground level and atop tall buildings were used for stationary samplings. Three mobile samplings were made by exposing bundles of seven test tubes in a holder at the front end of the hood of an automobile driven 100 to 500 or more miles for each sampling. Four samplings were made overnight on the outside of the non-worked vestibule door of Pullman cars in transit from Cincinnati to and from Detroit, 250 miles, and to and from Chicago, 300 miles, each way. Two samplings were made in the pair of metal tubes taped to the top and front end of Diesel locomotives in transit from Los Angeles to Chicago (2,250 miles). One stationary sampling was made for three days atop the 33rd story of an hotel in Detroit, and one during the day for 12 hours atop the 22nd story of an hotel in Chicago.* Three stationary samplings were made at ground level on the front lawn of the Receiving Building, Longview Hospital, Cincinnati, and three in the back yard of the writer's residence in the northern outskirts of Cincinnati.

The tubes containing the absorbent material were wrapped in paper towels and sterilized in the autoclave. Precautions were taken to prevent extraneous contamination such as from hands and breath of the operator in placing and removing the samples and cultures of exposed material were made in a non-stacked bacteriological hood.

The absorbent material consisted of pebbles coated with mineral oil in two samplings, glasswool in one and fiberglas in 14. Nine of these exposures were made during the latter part of March and the first two weeks of April, when the incidence of epidemic respiratory infection was still high, and eight were made during the last week in May and the first week in June, 1949, when the general incidence of respiratory infections was low. Mobile samplings totaled exposures in transit of altogether 6,900 miles in 12 states.

Pebbles and suitable portions of glasswool and fiberglas that had been exposed were planted directly into freshly prepared dextrose-brain broth. Washings of exposed pebbles, glass wool and fiberglas made respectively in 20 ml. of NaCl solution were similarly inoculated into freshly prepared dextrose-brain broth and as a control into corresponding dextrose-broth without the brain, and on blood-agar. Part of the washings were used for inoculation of mice and embryonated hen eggs before and after filtering through Seitz pads or through porcelain filters. Films of the sediment of centrifuged saline washings were stained by Gram's method and counterstained with a two per cent aqueous solution of safranine 0 for microscopical study. On the basis of results of previous experiments (1), the white mouse and embryonated eggs were used to determine the infectivity of the streptococci and the presence or not of filtrable agents or virus.

As a routine, four mice were inoculated under deep ether anesthesia; two cerebrally and nasally with .03 and .06 ml. respectively and two with .06 ml. nasally only. Cerebral inoculation was made first and nasal instillation second. Inoculation of filtrates and washings were usually repeated once, sometimes twice, at 4, 24 or 48 hours. Material inoculated into mice consisted (1) of washings of exposed material unfiltered and filtered, (2) of pure cultures of streptococci obtained from the end point of growth of serial-dilution cultures in dextrose-brain broth of exposed material and of emulsions of brains, lungs and gastro-intestinal contents of mice that had succumbed to or in which encephalomyelitis, pneumonitis or gastroenteritis respectively developed and (3) of emulsions and filtrates of emulsions of brains and lungs of mice in which encephalomyelitis or pneumonitis had developed and of filtrates of gastro-intestinal contents of mice in which gastroenteritis developed.

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Table 1
Results of partial-tension cultures in dextrose-brain broth and of aerobic cultures on blood-agar.

Material inoculated into mice whose lungs were cultured.	Isolation of streptococci from pneumonic lungs of mice following cerebral and/or nasal inoculation			
	In dextrose-brain broth		On blood-agar	
	Cultured	Percent positive	Cultured	Percent positive
NaCl solution washings of material exposed to outdoor air.	127	44	45	4
Streptococci isolated from washings of material, exposed to outdoor air, from involved brains, lungs and intestinal content of inoculated mice.	108	82	42	69
Emulsions of pneumonic lungs of inoculated mice.	252	79	77	26
Filtrates of washings of material exposed to outdoor air, and of emulsions of involved brains, lungs, and intestinal content.	187	60	75	3
Total	674	67	239	23

Only mice from healthy stock were used. The inoculated mice were observed two or three times a day and symptoms, if any, were recorded. Those that died were examined as soon after death as possible. Those that survived following inoculation of washings or filtrates of washings of exposed material from whatever source were etherized to death in from seven to 12 days and those that received dextrose-brain broth cultures or emulsions of brains and lungs on successive animal passages were anaesthetized to death in from three or five to eight days. Cultures of pipettings of emulsions of brains, lungs, intestinal contents and of exposed material were made in dextrose-brain broth and often as a control in corresponding dextrose broth without the brain and on blood-agar plates. All cultures were incubated at 33° C. Routinely, the supernatant portion of dextrose-brain broth containing 15 ml. of pure cultures of streptococci were poured into 12 ml. screw-capped vials, centrifuged and the sedimented streptococci were suspended in approximately 0.2 ml. of chemically pure glycerin, two parts, and saturated NaCl solution, one part, and stored in sealed 4 ml. screw-capped vials at 10° C. for agglutinative and other tests.

Agglutinative titers for the freshly isolated streptococci that had been preserved in this menstruum, of antistreptococcic serums prepared in horses (8), of thermal antibody prepared in vitro (8), and of convalescent and control serums of humans were determined at four fivefold dilutions of 1-20 to 1-2500 in saline solution containing .2 per cent phenol; 0.2 ml. of the antiserums, antibody solutions and convalescent serums respectively, and 0.2 ml. of the glycerin-NaCl solution suspensions of streptococci diluted to six billion per ml. in NaCl solution containing .2 per cent phenol were added to test tubes 1x7 cm., thoroughly shaken and placed at 45° C. for 18 to 24 hours, when readings were made (9). Slide-agglutination tests were made with types I, II and III pneumococcal antiserums. The degree of agglutination was recorded according to the arbitrary scale of 0 to 4 plus usually without reference to the source of the streptococci. In order to visualize readily the results of the large number of agglutinative tests, the percentage of the total possible agglutination in the four respective dilutions was determined. A 4 plus agglutination for each of the four dilutions, or 16/16 = 100 per cent. A total of 9 plus agglutination for the four dilutions, or 9/16 = 56 per cent, etc.

In order to check the results obtained in mice, emulsions and filtrates of emulsions and pure cultures of streptococci, of washings of materials exposed to outdoor air, of brains, lungs and intestinal contents of mice in which encephalomyelitis, pneumonitis or gastroenteritis had developed, were inoculated into embryonated chicken eggs. From 0.5 to 2 ml., depending upon the nature of the inoculum, whether cultures of streptococci undiluted or diluted up to 1-10,000, whether emulsions or filtrates of emulsions, were inoculated into the allantois or into the yolk sac of fertile eggs that had been incubated for 11 days. The incubated eggs were candled at the time inoculated and at 20 days, when the contents were examined and cultures were made of allantoic and yolk fluids.

RESULTS OF CULTURES OF MATERIAL EXPOSED TO OUTDOOR AIR AND OF TISSUES OF MICE INOCULATED

Streptococci grew in one or more tubes of dextrose-brain broth, usually in mixture with *B. subtilis* and less often with anaërobic gram-positive and aërobic gram-negative gas-forming bacilli in all of the 17 samplings cultured. Pure cultures of streptococci or

Table 2
Summary of experiments in mice inoculated cerebrally and/or nasally with material obtained from a sampling of outdoor air made atop a Diesel locomotive during transit from Los Angeles to Chicago, March 26-28, 1949.

Material Inoculated				Mice						
				Inoculated	Per cent that died	Incidence in percent of the development of pneumonic lungs			Streptococci from pneumonic lungs	
						Encephalomyelitis	Pneumonitis	Gastroenteritis	Cultured	Yielding streptococci (Percent)
Saline washings of exposed glasswool			Unfiltered	4	0	25	100	50	4	100
			Filtered	4	50	50	50	25	4	50
Filtrates of pneumonic lungs of mice following inoculation of the streptococcus isolated from exposed glasswool.				12	0	0	50	0	6	100
Dextrose-brain broth cultures of	Streptococcus isolated from	Exposed glasswool from the end point of growth of a serial dilution subculture at dilutions of	10^{-8}	8	25	100	25	25	2	100
			10^{-12}	8	13	38	50	0	4	100
			10^{-14}	8	13	13	100	13	6	100
		Emulsions of hemorrhagic lungs after one mouse passage in the	Primary culture	8	50	0	75	0	6	100
			Fourth subculture	8	25	38	50	0	4	100
	Diplostreptococcus	Ileum of mouse in the first passage		8	63	13	100	50	4	100
	Diphtheroid bacillus from washings of exposed glasswool.			4	0	0	0	0		
Total				72	24	29	56	14	40	95

diplostreptococci grew in 21 of 124 tubes of dextrose-brain broth inoculated from 12 of the samplings. Pure cultures were obtained from the end point of growth of serial dilution cultures in dextrose-brain broth in the remaining five samplings. Streptococci grew from each of 10 samplings in one or more tubes of dextrose-brain broth and in only three of the samplings in dextrose-broth. The incidence of isolations of streptococci in dextrose-brain broth and on blood-agar of the different materials cultured are summarized in Table 1. It will be seen how far superior dextrose-brain broth was than blood-agar, especially in the case of saline washings and filtrates. Serial-dilution cultures of washings of exposed material in dextrose-brain broth made always at dilutions of 1/10,000 or 10^{-4} from tube to tube with a nichrome wire sterilized in the flame at each dilution yielded pure cultures of streptococci in six samplings at 10^{-6} dilutions when cultures on blood-agar of the undiluted washings proved sterile. Pure cultures of the streptococci were often obtained at 10^{-10} dilutions and sometimes at dilutions of 10^{-14} from the primary or subsequent pure cultures in dextrose-brain broth (6).

Diplococci or streptococci were found in small numbers in stained films of the sediment of centrifugated washings of materials exposed to outdoor air, but always in numbers far fewer than as indicated by serial-dilution cultures in dextrose-brain broth. The streptococci isolated directly from outdoor air and from the brain and lungs of inoculated mice and embryonated eggs were alike in morphology, virulence and in serologic properties. They were all gram-positive and of the nonhemolytic type. They produced small grayish, non-adherent, sometimes slightly green colonies on blood-agar. The diplostreptococcus, on isolation, having elective affinity for the gastro-intestinal tract was larger than the streptococcus having affinity for the lungs, but after mouse passage, it could not be differentiated morphologically from the streptococcus.

Gas-forming gram-negative bacilli, presumably *B. aerogenes* and gram-positive bacilli resembling *B. subtilis*, grew from most samplings. Gram-positive gas-forming bacilli resembling *B. welchii* grew in seven. Gram staining micrococci grew in only three instances. *B. pyocyaneus*, bacilli with large end spores resembling *B. tetani*, diphtheroid bacilli, and type II pneumococcus grew each in only two instances and hemolytic streptococci in only one instance.

RESULTS IN MICE

The results obtained in mice following inoculation of the saline washings, unfiltered and filtered, of dextrose-brain broth cultures of the streptococcus in serial dilutions of emulsions and filtrates of emulsions of pneumonic lungs and of the diplostreptococcus from hemorrhagic ileum of a mouse in the case of a sampling made in March, 1949 atop a Diesel locomotive in transit from Los Angeles to Chicago are summarized in Table 2.

Encephalomyelitis developed in 21, or 29 per cent; pneumonitis in 40, or 56 per cent, and gastroenteritis in 10, or 14 per cent, of 72 mice inoculated. The streptococcus was isolated in 38, or 91 percent, of 40 pneumonitic lungs cultured. Cultures in dextrose-brain broth of the 16 filtrates inoculated proved sterile in all but three, but the streptococcus was isolated in pure culture from hemorrhagic pneumonic lungs which developed following inoculation of the "sterile" filtrates in high incidence. The incidence of encephalomyelitis decreased from 100 to 38, to 13 per cent and that of pneumonitis increased from 25 to 50 to 100 per cent in mice receiving increasing serial dilutions respectively of 10^{-8}, 10^{-12} and 10^{-14} of a culture of the streptococcus in the dextrose-brain broth in the second culture generation as isolated from the exposed glass wool. The results obtained with this sampling are included in Table 3.

The incidence of lesions of the brain, lungs and gastro-intestinal tract of mice following inoculation of the unfiltered and filtered NaCl solution washings and the streptococcus isolated from unfiltered washings of the 10 samplings of outdoor air made during March-April, when the incidence of epidemic respiratory in-

Table 3

Results in mice following cerebral and/or nasal inoculation of unfiltered and filtered saline washings and of streptococci isolated in dextrose-brain broth from washings of material that had been exposed to outdoor air in relation to the seasonal incidence of respiratory infections.*

Materials Inoculated		Time of samplings 1949	Incidence of respiratory infection	Inoculations inoculated	Mice					
					Inoculated	Percentage in which there developed			Streptococci from lungs	
					No.	Per cent that died	Encephalomyelitis	Pneumonitis	Gastroenteritis	No. cultured	Percent yielding filtrato-
Saline washings of absorbent material after exposure to outdoor air (17 samplings)	Unfiltered that yielded streptococci	March April	High	9	36	11	5	[77]	5	25	[96]
		May June	Low	5	12	0	0	8	0	12	0
	Filtered	March April	High	12	52	0	11	[84]	3	48	[33]
		May June	Low	5	20	5	0	15	0	19	31
	Streptococci from,	March April	High	20	76	10	13	[76]	0	56	[93]
		May June	Low	11	32	62	15	18	0	20	25
Total test material from outdoor air	10 samplings	March April	High	41	164	8	10	[79]	2	129	[89]
	7 samplings	May June	Low	21	64	4	7	15	0	51	21
Controls**				14	66	0	0	5	0	30	6

*Aside from a slightly greater incidence of deaths and of encephalomyelitis in mice that were inoculated cerebrally and nasally than in an equal number that received nasal inoculations only, the results were so nearly alike that the totals of the two groups are given in the tabulation.

**Unfiltered and filtered washings of unexposed material, unfiltered washings that did not yield streptococci, sterile dextrose-brain broth brought to the acidity of streptococcal cultures of NaCl solution.

fections was high, and of seven samplings made during May-June, when respiratory infections had largely disappeared, are depicted in Table 3. It will be seen that the incidence of pneumonitis following inoculation of unfiltered and filtered washings and of the streptococcus and the isolation of streptococci from the induced pneumonic lungs from samplings made during March-April was consistently much higher than from the seven samplings made during May-June. The total averages for pneumonitis were 79 and 15 per cent and for isolations of streptococci from involved lungs 89 and 21 per cent, respectively. This striking difference in incidence of pneumonitis and isolations of streptococci from involved lungs of mice inoculated during March-April and May-June with unfiltered material was also strikingly true for filtered saline washings. The averages were 84 and 15 per cent for pneumonitis and 83 and 31 per cent, respectively, for isolation of streptococci from lungs.

The results following inoculation of emulsions, filtrates of emulsions, and the streptococcus isolated from brains and lungs of mice in which encephalomyelitis or pneumonitis had developed, and of filtrates and streptococci isolated from contents of stomach and intestines of mice in which gastroenteritis developed are summarized in Table 4. The incidence of deaths of 16 per cent of 721 mice inoculated was relatively low throughout. The incidence of encephalomyelitis, while low, was uniformly higher following inoculation of emulsions, filtrates and streptococci from affected brains (25, 13, 36 per cent) than following inoculation of emulsions, filtrates and streptococci from affected lungs (9, 0, 12 per cent). The incidence of pneumonitis was relatively high throughout and was much higher in mice receiving emulsions, filtrates and streptococci from lungs (84, 81, 90 per cent) than those receiving like material from brains of inoculated mice (59, 25, 57 per cent). The incidence of gastroenteritis was high in mice that received filtrates and streptococci from contents of stomach and ileum of mice in which gastroenteritis had developed. The total average percentage incidence of encephalomyelitis, pneumonitis and gastroenteritis was 8, 74 and 12, respectively, of the 721 mice inoculated with the different test materials. The incidence of isolations of streptococci in dextrose-brain broth from hemorrhagic pneumonic lungs that developed following inoculation of emulsions and filtrates of emulsions of brains, lungs and content of stomach and ileum of mice in which encephalomyelitis, pneumonitis and gastroenteritis, respectively, had developed, was uniformly high and consistently greater following inoculation of material from lungs than from brain; and both higher in case of emulsions and of the streptococcus than following inoculation of filtrates.

A summary of results of cultures in dextrose-brain broth from filtrates as inoculated into mice and from emulsions of involved brains, lungs and gastro-intestinal contents following inoculation of filtrates is shown in Table 5. Isolation of the streptococcus was uniformly much higher from the respective tissues than directly from the filtrates. It was isolated from only 12, or 15 per cent, of 79 filtrates, and from 156, or 58 per cent, of 286 involved brains, lungs and gastro-intestinal contents cultured following inoculation of the 79 filtrates. Parallel cultures on blood-agar plates of the 79 filtrates proved negative.

In order to determine more precisely than by cerebral and/or nasal inoculation the possible epidemiologic importance of air-borne streptococci, mice were exposed to nebulized dextrose-brain broth cultures of seven freshly isolated strains. Ten mice weighing from 15 to 20 grams were placed into each of three metal-walled segregated cages, 8x8x11 inches. Into two of these cages were nebulized 5 ml. of 18 hour and 12 hour dextrose-brain broth cultures and into the third, dextrose-brain broth brought to the acidity of the cultures. Nebulizations were repeated once in 12 hours. The screened doors of the cages were sealed with cloth and the operator wore a gas mask during the duration of the nebulization. The animals were anaes-

Table 4

Results in mice following cerebral and/or nasal inoculation of emulsions and filtrates of emulsions and of streptococci from brains, lungs, and contents of stomach and ileum of mice in which encephalomyelitis, pneumonitis or gastro-enteritis respectively developed after from one to ten mouse passages of material containing streptococci isolated from samplings of outdoor air during March and April, 1949.

Materials Inoculated		Specimens Inoculated	Mice Inoculated		Mice Percent in which there developed			Streptococci from lungs	
			No.	Per cent that died	Encephalomyelitis	Pneumonitis	Gastroenteritis	Number cultured	Percent yielding streptococci
Emulsions of	Brain	14	59	24	25	59	19	45	60
	Lungs	35	140	26	9	84	11	94	76
Filtrates of emulsions of	Brain	4	16	0	13	25	0	16	31
	Lungs	37	150	12	0	81	0	138	61
Streptococci isolated from emulsions of	Brain	8	30	7	36	57	0	20	80
	Lungs	29	116	13	12	90	0	104	92
Filtrates of	Contents of stomach and ileum	17	68	21	2	59	22	40	45
Streptococci isolated from		35	142	11	3	65	31	54	67
Total		179	721	16	8	74	12	511	69
Control*		28	114	0	0	6	0	48	7

*Emulsions and filtrates of emulsions of brains and lungs of normal uninoculated mice (38 mice), filtrates of contents of stomach and ileum and lungs of normal mice, freshly prepared and after incubation for 48 hours without and with streptococci (47 mice), sterile dextrose-brain broth and NaCl solution (29 mice).

thetized to death with ether four days after the first nebulization. A mixture of freshly isolated streptococci in the third rapidly repeated subculture in dextrose-brain broth from six samplings made in the midwest during March was nebulized into the first cage. Pneumonitis was found in eight of the 10 mice thus exposed. The streptococcus nebulized into the second cage was isolated from the fiberglas of one of the tubes exposed during the second sampling atop the Diesel locomotive in transit, April 21-23, for 2,250 miles, after storage at room temperature for one month. Pneumonitis developed in seven of the 10 mice exposed to this strain. Sterile dextrose-brain broth brought to the acidity of the streptococcal cultures was nebulized into the third cage of 10 mice. Pneumonitis was absent in all.

In order to determine certain underlying properties of pneumotropic streptococci perhaps responsible for their predilection for and necrotizing action in lung tissue, the living and heat killed streptococcus and the filtrate of the living culture of one highly pneumotropic strain were each inoculated nasally into four mice (not included in tables). Pneumonitis in varying degree developed in all, but was most marked in the four inoculated with the living culture.

Of altogether 945 mice that received cerebral and/or nasal inoculations, 79 developed symptoms referable to the central nervous system, resembling strikingly those of certain diseases that occur in persons, especially following respiratory infections and following epidemics of influenza, as follows: severe lethargy in nine, great hyperirritability in 18, disorientation in seven, severe tremors and spasms of muscles and ataxia in 13, convulsive seizures in eight, general rigidity in eight and flaccid paralysis in 16. Moderate congestion of brain and meninges were found at necropsy in all mice having symptoms of encephalomyelitis. Those that had convulsive seizures had edema and ischemia of the cerebral cortex. Abscess formation occurred in only two instances, due to *B. bronchisepticus*. The different types of symptoms and lesions noted in these mice in low incidence were similar to those produced in other experiments in much higher incidence with respective specific types of streptococci isolated in studies of encephalitis, multiple sclerosis, poliomyelitis, schizophrenia and epilepsy.

The degree of lesions of lungs of mice varied greatly from intense widely disseminated interspersed areas of hemorrhagic edema and emphysema of greatly dilated lungs in the early stages with large and small areas of consolidation somewhat later. Lobar distribution of consolidation occurred rarely and exudative pleuritis was not observed. Lesions of the gastro-intestinal tract were limited to scattered hemorrhages in the mucous membrane of the acid-secreting portion of the stomach and to hemorrhagic chocolate-colored mucus of extremely congested small intestine, involving especially the ileum. Lesions of colon associated with diarrhea were not observed.

ILLUSTRATIVE EXPERIMENTS AND PROTOCOLS

Mouse 1 was inoculated cerebrally with .03 ml. and nasally with .06 ml. respectively April 1, 2, 3 and 4, 1949, of the NaCl solution washing of exposed glass wool of the sampling referred to in Table 2. It remained seemingly well and was anaesthetized to death April 11. Large and several small areas of broncho-pneumonia involving both lungs were found. The pleura, brain and other viscera were normal. Cultures from emulsion of the lungs in dextrose-brain broth yielded a pure culture of the streptococcus while those on blood-agar proved sterile. Three other mice similarly inoculated and anaesthetized revealed varying degrees of pneumonitis and no lesions elsewhere.

Mouse 2, one of four mice, was inoculated at the same time and in the same manner as Mouse 1, but with a Seitz filtrate of the NaCl solution washings of the exposed glass wool. April 5, it had developed generalized tremors and twitchings of the eyelids and muscles of the ears. April 6, the twitchings continued and weakness of extremities had developed. April 7, it was found dead. Necropsy revealed congestion of the brain, hemorrhagic edema and broncho-pneumonia of both lungs, hemorrhagic mucus and hemorrhages in the acid secreting portion of the stomach, hemorrhagic mucus in the lumen of the distal portion of the ileum with punctate hemorrhages in the mucus membrane. The results in the three accompanying mice were similar.

Serial dilution cultures in dextrose-brain broth of the hemorrhagic mucus in stomach and ileum yielded a pure culture of the diplostreptococcus at the end points of growth and blood-agar plates revealed gram-positive and negative bacilli and large numbers of small grayish non-adherent colonies of streptococci.

Mouse 3, one of 12 mice, was inoculated April 5, 1949 cerebrally with .03 ml. and nasally with .06 ml. of the dextrose-brain broth culture of the streptococcus isolated from the filtrate that was inoculated into Mouse 2. It remained apparently well and was anaesthetized to death April 8. The brain, stomach and intestines were normal, while the lungs revealed large areas of hemorrhagic broncho-pneumonia.

Table 5

Results of cultures of filtrates before inoculation into mice and of emulsions of involved brains, lungs, and gastro-intestinal contents following inoculation of filtrates.

Source of Material Inoculated			Isolation of streptococci in dextrose-brain broth from: Filtrates as inoculated into mice. Cultured	Filtrates as inoculated into mice. Percent +	Emulsions of involved brains, lungs and gastro-intestinal contents following inoculation of filtrates. Cultured	Emulsions of involved brains, lungs and gastro-intestinal contents following inoculation of filtrates. Percent +
Filtrates of saline washings of material exposed to outdoor air			21	19	52	81
Filtrates of emulsions of	Brains of mice in which encephalomyelitis	Developed following injection of respective filtrates	4	0	16	31
	Lungs of mice in which Pneumonitis		37	13	178	58
	Contents of stomach & ileum in which Gastro-enteritis		17	17	40	45
Total*			79	15	286	59

*Parallel cultures on blood-agar plates of the 79 filtrates before inoculation were all negative.

Cultures from the lungs yielded a pure growth of the streptococcus. Seven of the remaining 11 mice showed similar results.

Mouse 4 was inoculated May 10 and 11, 1949 cerebrally with .03 ml. of a Berkefeldt V filtrate of a 1-10 dilution of the allantois of five embryonated eggs in which the embryo had died following inoculation of a filtrate of emulsion of pneumonic lungs of two mice that had received the streptococcus isolated from the sampling of outdoor air referred to in Table 2. The filtrate inoculated into Mouse 4, May 10 and 11, yielded the streptococcus in pure culture in dextrose-brain broth and no growth occurred in dextrose-broth nor in blood-agar. The mouse remained apparently well and was killed with ether May 16. Areas of hemorrhagic consolidation were found in both diaphragmatic lobes and in the cardiac lobe. Cultures in dextrose-brain broth of an emulsion of the pneumonic lungs yielded the streptococcus in pure culture and cultures on blood-agar proved sterile. Pneumonitis developed in two of three additional mice similarly inoculated.

Mouse 5, one of four mice, was inoculated January 25, 1949 cerebrally with .03 ml. and nasally with .06 ml. of an 18 hour dextrose-brain broth culture from a chick-embryo culture made February 16, 1948 of a streptococcus that had high pneumotropic virulence as isolated from outdoor air during a severe epidemic of influenza and which was stored in the dark at room temperature meanwhile (2-16-48 to 1-25-49). January 26, the mouse was excitable and jumpy on prodding. January 27, the animal was extremely excitable. It dashed about wildly in spells when prodded and at irregular intervals otherwise. January 28, it was still excitable, the respirations were increased and was seen to die in a generalized tonic spasm. Necropsy revealed severe diffuse congestion of the brain and dilated lungs with widely disseminated interspersed areas of hemorrhagic edema and emphysema. Cultures from brain and lungs on blood-agar and in dextrose-brain broth yielded a pure culture of the streptococcus. Similar symptoms developed in two of the remaining three mice.

Mouse 6 was inoculated February 16, 1949 cerebrally with .03 ml. and nasally with .06 ml. of an emulsion of a pneumonic lung of a mouse that had received the filtrate of an emulsion of a pneumonic lung produced with the third mouse passage of the streptococcus referred to in protocol of Mouse 5. February 7, the animal appeared well. February 18, severe generalized tremors and slight spasms of the muscles of the left fore leg and shoulder were noted. February 19, recurring convulsive seizures resembling status epilepticus had developed in which respirations ceased repeatedly for a short time at the height of the seizures and then were resumed as convulsive seizures disappeared. It was seen to die in a violent generalized convulsion. Necropsy done at once revealed no mark in the brain at the point of injection, an ischemic edematous cerebral cortex, normal lungs and other viscera. Cultures from the brain in dextrose-brain broth yielded a pure culture of the streptococcus.

Mouse 7 was inoculated September 1 and 2, 1949 with .03 ml. of a Berkefeldt V filtrate of emulsions of the brains of eight mice that had received emulsions or filtrates of emulsions of the brains of mice on successive passage after initial inoculation for the first mouse passage of a streptococcus originally pneumotropic as isolated from outdoor air in winter during an epidemic of influenza and which had changed to neurotropic type in a chick-embryo culture on storage at room temperature in the dark into summer. September 3, the animal had developed tremors and was abnormally quiet and responded minimally to proddings. September 4, the animal was lethargic, did not respond to proddings and as it was turned on its side, the extremities were held extended in greatly increased tonus. September 5, it was still lethargic or semi comatose. The tremors had become less pronounced and weakness of the extremities had clearly developed. When lying on its side it held extremities outstretched in increased tonus. September 6, it was found dead. Necropsy revealed no mark at the point of injection, diffusely congested brain and meninges, normal lungs and other viscera. Dextrose-brain broth cultures of the brain revealed the streptococcus while blood-agar plates remained sterile. Four of five other mice similarly inoculated developed lethargy, increased tonus and finally weakness of muscles of extremities.

Mouse 8 was inoculated April 1, 1949 cerebrally with .03 ml. and nasally with .06 ml. of a streptococcus in the fourth subculture and from a serial dilution culture in dextrose-brain broth at a dilution of 10^{-12}. The streptococcus was isolated originally from outdoor air in January, 1948 during a severe epidemic of influenza and which had been kept at room temperature in a chick-embryo culture meanwhile. April 2, it had developed flaccid paralysis of hind extremities which it dragged limply along with fore extremities. April 3, flaccid paralysis of hind and severe paralysis of fore extremities had developed. The respirations were extremely rapid. It was killed with ether as dying from respiratory failure. Necropsy revaled moderately congested brain, a greatly softened spinal cord and normal lungs. Dextrose-brain broth and blood-agar cultures yielded the streptococcus. The results in two of three additional mice inoculated were similar to those of Mouse 8.

Mouse 9, one of four mice, was injected April 4, 1949 cerebrally with .03 ml. and nasally with .06 ml. of a dextrose-brain broth culture of the streptococcus in the second culture representing a 10^{-16} dilution of original inoculum isolated from outdoor air. April 5, severe tremors and slight clonic spasms of extremities had developed. April 6, it had recurring spasms. April 7, the animal was extremely excitable, kept running about in aimless fashion and repeatedly jumped up at sides of cage. When prodded, it developed generalized convulsions. April 8, it was less restless, usually sat quietly humped up. It was found dead at 4:00 p. m. The brain was severely congested while the lungs were normal. There was no mark at the site of injection. The meninges were moist and shiny. The streptococcus was isolated from the brain in dextrose-brain broth while blood-agar platings remained sterile. Similar results occurred in two of the remaining three mice.

Table 5

Results following allantois- and yolk-sac inoculation of embryonated chicken eggs with NaCl solution washings and filtrates of washings of, and streptococci from material exposed to outdoor air and of streptococci, emulsions, and filtrates of emulsions of pneumonic lungs of mice and of allantoic fluid on successive passage through mice and embryonated eggs, and of agglutination of chicken erythrocytes.

Material Inoculated		Specimens	Embryonated eggs inoculated into allantois or yolk sac			Washed chicken erythrocytes plus allantoic fluid of inoculated eggs in which the embryo died			
			Inoculated	Embryos that died	Streptococci from allantoic fluid of eggs in which embryo died	Specimens, allantoic fluid of test and control eggs	No. in which agglutination occurred at dilutions of allantoic fluid of		
							1-5	1-20	1-200
NaCl solution washings of material of three samplings of outdoor air, April, 1949	Unfiltered	3	7	7	7	7	6	6	5
	Filtered		7	6	2	6	4	4	3
	Streptococci isolated		12	12	12	7	2	5	4
Streptococci from pneumonic lungs of inoculated mice and allantoic fluid of eggs in which the embryo died		7	14	10	10	7	2	5	4
Emulsions of pneumonic lungs of mice and allantoic fluid of inoculated eggs in which the embryo died		6	12	12	12	16	7	6	6
Filtrates of emulsions of pneumonic lungs of mice and allantoic fluid of inoculated eggs in which the embryo died		13	26	17	16	17	10	8	11
Total		29	78	64	59	60	31	34	33
Control: NaCl solution washings of unexposed fiberglas, emulsions and filtrates of emulsions of normal mouse lungs and allantoic fluid of eggs containing living embryos.			23	2	0	17	9	3	1

Owing to the high incidence of lesions of lungs of mice, following inoculation of NaCl solution washings of material exposed to outdoor air of the streptococci, of emulsions and filtrates and their similarity to those which follow inoculation of influenzal virus (4), it was decided to study the effects of these on embryonated chicken eggs.

RESULTS OF INOCULATION OF EMBRYONATED CHICKEN EGGS AND OF AGGLUTINATING ACTION OF ALLANTOIC FLUID OF EGGS IN WHICH THE EMBRYO DIED

The materials inoculated into the allantois and yolk sac and results obtained in seven to 11 day embryonated chicken eggs are summarized in Table 6. The incidence of deaths of embryo and of isolations of streptococci from allantoic fluid was high and comparable following inoculation of unfiltered and filtered saline washings of material exposed to outdoor air, of cultures of streptococci, of emulsions and filtrates through from two to five consecutive egg passages. Isolation of streptococci following inoculation of emulsions containing streptococci and of the streptococcus was uniformly high while after inoculation of filtrates of washings of exposed material was two of six, while following inoculation of filtrates of emulsions of pneumonic lungs of mice and of allantoic fluid was 16 of 17.

The method of Hirst (10) was used to determine the agglutinative action on suspensions of washed chicken erythrocytes of allantoic fluid of embryonated eggs in which the embryo had died. No agglutination occurred in one hour. The washed erythrocytes to which increasing dilutions of allantoic fluid of eggs in which the embryo died and of allantoic fluid of control eggs containing the living embryo settled at the same rate with no evidence of agglutination of red cells. However, it was found that on inverting the tubes after standing at room temperature for 24 hours, a variable degree of agglutination from small but easily visible friable clumps to a tenacious gelatinous mass of unhemolyzed or hemolyzed erythrocytes flat on top and rounded at the bottom had formed at the bottom in some of the tubes containing progressive dilutions of test material. Such agglutinative action at dilutions of 1-5, 1-20 and 1-200 of test and control material are indicated in the second half of Table 6. The tenacious agglutinated mass of erythrocytes was often absent in the low dilutions of allantoic fluid and occurred repeatedly in additional experiments with increasing dilutions, even at dilutions of 1-2000. A variable degree of such delayed agglutination was produced alike by the allantoic fluid of eggs in which the embryos had died following inoculation of streptococci, emulsions and filtrates and which did not occur or occurred in far lower incidence in control experiments. This delayed agglutination was obtained in experiments only after allantoic fluids had been stored at 10° C. for 10 to 30 days.

RESULTS OF EXPERIMENTS ON SEROLOGIC PROPERTIES OF STREPTOCOCCI ISOLATED FROM OUTDOOR AIR

The results of a large number of experiments to determine the agglutinative titer of streptococcic antiserum and streptococcic thermal antibodies (9) prepared from strains of streptococci isolated from persons having poliomyelitis or respiratory infection and of pooled serums from persons convalescing from poliomyelitis or respiratory infection respectively and of thermal antibody for streptococci isolated from outdoor air, as isolated and after passage in mice and embryonated eggs are summarized in Table 7.

It will be seen that the streptococci isolated from outdoor air in summer, 1948 and 1949 and from the brain of mice inoculated with strains isolated from outdoor air were uniformly agglutinated in higher titer by antiserum and thermal antibody prepared with streptococci isolated in studies of poliomyelitis and by the serum of persons convalescing from poliomyelitis than by antiserum and antibody prepared with streptococci isolated in studies of respiratory infection and by the serum from persons convalescing from such infection. In sharp contrast, the streptococci isolated from outdoor air in winter, 1948 and 1949 and in spring of 1949 and from pneumonic lungs of inoculated mice and from the allantoic fluid of embryonated eggs were uniformly agglutinated in highest titer by the antiserum and thermal antibody prepared with streptococci isolated in studies of respiratory infections and by the serum of persons convalescing from such infection than by antiserum and thermal antibody prepared from streptococci isolated in studies of poliomyelitis and by the poliomyelitic convalescent serum. The diplostreptococcus isolated from stomach and ileac contents of mice in which gastroenteritis developed were agglutinated maximally by thermal antibody prepared from the diplostreptococcus isolated in studies of infectious gastroenteritis.

Table 7

Agglutinative titer of streptococcic antiserums and thermal antibody and of convalescence serums for streptococci isolated from outdoor air as isolated and after mouse and embryonated egg passage.

Antiserums and thermal antibodies prepared from streptococci isolated from persons ill, from outdoor air, and serums of persons convalescing from poliomyelitis and respiratory infections respectively.		Percentage of total possible agglutination by antiserums, thermal antibodies and convalescence serums at 4 fivefold dilutions of 1-20 to 1-2500 of streptococci isolated from								
		Outdoor air					Outdoor air, 1949			
		As isolated in					After passage through			
		Winter		Summer	Spring	Summer	Mice			Embryonated eggs
							As isolated from			
		1948	1949	1948	1949	1949	Brains	Lungs	Stomach & ileac contents	Allantoic fluid
		(4342)	(4238)	(5193)	(569)	(15212)	(5297)	(4879)	(1278)	(5249)*
Antiserums	Poliomyelitis	2	5	66	0	67	16	5	0	8
	Respiratory infection	33	33	31	17	41	22	79	30	32
	Arthritis	1	1	15	0	27	11	8	8	12
Thermal antibodies	Poliomyelitis	23	26	83	22	32	23	22	20	32
	Respiratory infection	52	64	48	50	25	36	53	43	61
	Encephalitis	24	29	37	25		26	24	34	27
	Gastro-enteritis	28	36	45	30		37	32	64	42
	Streptococci outdoor air winter, 1949 which produced: Encephalomyelitis	28	49	64	32		41	23	38	43
	Pneumonitis	57	68	34	64		43	55	47	53
Convalescence serums	Poliomyelitis 5-10 days	3	1	34	0		15	3	0	4
	11 days plus	4	4	64	0	32	22	0	2	8
	Respiratory infection according to cutaneous antibody-titer: Low	23	38	15	18		15	17	13	24
	High	33	43	20	25		20	22	18	32
	Control, Normal human serum	0	3	0	3		3	2	0	0

*The figures in parentheses indicate respectively, strains, cultures before or after mouse-passage and suspensions of the streptococci used in agglutinative tests.

The streptococci isolated from outdoor air in winter and spring, from the pneumonic lungs of inoculated mice and from the allantoic fluid of embryonated eggs were agglutinized maximally by thermal antibody prepared from streptococci isolated from outdoor air in winter. Eighty-three of the 120 suspensions summarized in Table 6 were subjected to the slide-agglutinative test with Types I, II and III pneumococcal antiserums. Eleven of these were agglutinated by Type II and none by Type I or III antiserums.

SUMMARY AND COMMENTS

The results of a bacteriological study made of outdoor air in winter and spring, 1948 and 1949, during epidemics of respiratory and gastro-intestinal infections, are reported.

Nonhemolytic streptococci and diplostreptococci were isolated in the highly favorable medium, dextrose-brain broth, from each of the 17 samplings made during train and automobile transit or on weather vanes in 15 midwestern and western states. The incidence of pneumonitis, of encephalomyelitis and of gastroenteritis in inoculated mice paralleled roughly the incidence of spontaneously occurring respiratory infections, encephalomyelitis and gastroenteritis current in human beings at the time, being high during March-April and low during May-June. The abrupt change in virulence in streptococci noted in this study is in accord with changes which occurred seasonally, and on successive animal passage in streptococci reported previously (1, 11, 12).

The phenomenon of dissociation or mutation was strikingly shown in these experiments. Changes in incidence of encephalomyelitis, pneumonitis and gastroenteritis occurred under stress of progressive serial dilution cultures (Table 2) and on successive mouse and egg passage of the streptococcus. Filtrates of NaCl solution washings of material exposed to outdoor air, of suspensions of pneumonic lungs, encephalitic brains and gastro-intestinal contents of mice sterile to dextrose-brain broth produced pneumonitis, encephalomyelitis and gastroenteritis and death of embryos respectively in significant incidence and the streptococcus was in turn isolated in dextrose-brain broth from the tissues involved. The tissues for which the filtrable or perhaps a submicroscopic or "virus" phase of the streptococcus had elective affinity, apparently afforded conditions more favorable for growth or transformation of submicroscopic filtrable forms into the large non-filtrable cultivable streptococcus than did dextrose-brain broth.

The streptococci as isolated from samplings and from lungs after successive passage through mice and embryonated chicken eggs were agglutinated maximally by antiserums and thermal antibody prepared with streptococci isolated from persons having epidemic respiratory infections and by the pooled serums of persons convalescing from such infections. The streptococci isolated from the brain of mice in which encephalomyelitis developed were agglutinated in far higher titer by antiserums and thermal antibody prepared from streptococci isolated from persons having encephalitis or poliomyelitis and by the pooled serums of persons convalescent from poliomyelitis than the strains isolated from pneumonic lungs or embryonated eggs. The strains isolated from the intestinal contents of mice in which gastroenteritis developed were agglutinated maximally by thermal antibody prepared from the diplostreptococcus isolated in studies of epidemic gastroenteritis (3).

The streptococci isolated from pneumonic lungs of mice and from allantoic fluid of embryonated eggs following inoculation of saline washings and filtrates of washings, of cultures of material exposed to outdoor air, of emulsions of pneumonic lungs and filtrates of such emulsions were culturally and morphologically alike. Cultures from lungs of mice and of allantoic fluid of embryonated eggs inoculated as controls proved negative. The possible "pick-up" of a spontaneously occurring virus in mouse lungs was excluded by the nature of the experiments, including the absence of deaths from and of spontaneously occurring pneumonitis in mouse stocks during the course of these many experiments, by the controls, by the isolation of specific types of streptococci and by the experiments in embryonated eggs.

The presence in washings of exposed material and hence in outdoor air of streptococci and of filtrable forms capable of growing into streptococci in numbers far greater than was shown by stainable forms in smears of the centrifuged sediment and by the number of colonies that grew on blood-agar plates (6) was shown in serial dilution cultures in dextrose-brain broth.

A filtrable agent resembling influenza virus has been produced from pneumotropic streptococci (4). The virus of influenza has since been shown to be particulate with the electron microscope. The particles consist of spheres or ovoids and occur singly, in diplo and filamentous or chain formation resembling in important respects the cultivable streptococcus but approximately one twelfth to one twentieth its size (13, 14). The results of these studies, the production of filtrable forms of staphylococci (15), proteus vulgaris and other organisms by Tulasne (16) and the observations on the importance of nonhemolytic streptococci in "virus" or atypical pneumonia (7) are in accord with results reported herein.

The data adduced indicate (1) that nonhemolytic streptococci, diplostreptococci and related filtrable agents in outdoor air in winter during epidemics of respiratory and gastro-intestinal infections have importance in the pathogenesis of influenza, other respiratory infections, of encephalomyelitis and of gastroenteritis, and (2) that the filtrable agents demonstrated in outdoor air, apparently for the first time, are phasally related to the cultivable streptococci and diplostreptococci and perhaps to the viruses of influenza, encephalomyelitis and gastroenteritis.

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RESPONSES OF THE GUINEA PIG'S ILEUM TO HISTAMINE, ACETYLCHOLINE, ANTIGEN, AND ELECTRICAL STIMULATION AS INFLUENCED BY PROGRESSIVE DECREASES IN THE CONCENTRATIONS OF CALCIUM, MAGNESIUM, OR POTASSIUM SEPARATELY OR IN PAIRS

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THE PRESENT WORK sought to establish whether the responses of the guinea pig's ileum to histamine dihydrochloride, acetylcholine bromide, antigen (horse serum), or electrical stimulation might be influenced at different rates by progressive decreases in the concentrations in the perfusing Locke's solution of calcium, magnesium or potassium ions, separately or in pairs. It was thought some insight into the mechanism of action of these drugs might be gained if significant qualitative or quantitative differences in the effects of the ion-deficient solutions upon the responses to the four stimulating agents could be demonstrated. Since the initial studies of Ringer (1), concerning the optimal concentrations of common cations required for physiological perfusing fluids, a voluminous literature has accumulated pertaining directly or indirectly to this subject. To attempt its review in this paper would be inappropriate, if not impossible. Nonetheless, a survey of the literature failed to reveal a study comparable in nature or purposes to the one herein reported.

METHODS

The apparatus and general procedure employed in this study have been previously described in detail (2). Initially the 2 cm. strip of ileum from the guinea pig was perfused with Locke's solution of the composition recommended by Cantoni and Eastman (3). Oxygen with five per cent carbon dioxide was employed for the continuous oxygenation of the tissue and the maintenance of the pH.

Sub-maximal, duplicable control responses to histamine, acetylcholine, and electrical stimulation were elicited. For electrical stimulation, a tetanizing current supplied by a Harvard inductorium connected to the two ends of the ileal strip by platinum electrodes was utilized. Since sensitized gut† seldom responds more than once to added antigen, and almost invariably with marked decrements in the response if it does yield more than one, a somewhat different approach to the problem of studying that stimulant had to be adopted. Antigen was usually added but once to any given strip of gut, since rarely did its later addition evoke much, if any, response. The response to that first addition was taken as evidence that other strips of gut from the same sensitized animal had likewise been sensitized. This was open to the obvious objection that the response to antigen of even contiguous strips of gut from a sensitized guinea pig can vary markedly. We were still obliged to adopt the method noted, since no suitable alternative occurred to us. Danielopolu (4) has described repeated like responses to additions of the antigen to the same strip of gut from a sensitized rabbit. They were attained by adding sizable doses of acetylcholine to the bath between each addition of antigen and allowing a brief interval for the tissues to absorb the added drug. Despite an extensive series of experiments in which the doses of acetylcholine and antigen were widely varied as well as the interval during which the tissue was in contact with the acetylcholine, we never succeeded in satisfactorily duplicating his results. Additions of choline chloride yielded somewhat better results than the acetylcholine but by no means permitted duplicable, maximal responses to successive doses of antigen. The cause of this discrepancy is obscure but is probably to be sought in the different strains of animals, in diet, in the mode of sensitization, in the nature of the perfusion fluid, etc.

Once suitable control responses had been elicited, the bottle of normal Locke's solution was replaced by a bottle lacking the single ion or pair of ions under study. The normal perfusion fluid was then washed out of the bath proper and the ion-deficient solution admitted in its place. After several minutes, the responses of the gut to acetylcholine, histamine, and electrical stimulation were again determined. This process was repeated until several successive

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†The guinea pigs (300-350 gms.) were sensitized to horse serum by a subcutaneous injection of 0.5 ml. three weeks prior to use.

washings and drug additions revealed no further changes in the responses. The missing ion was then added in increasing increments directly to the bath with drug additions after each increment. Once it had been established that further additions of the ion did not alter the responses or else exerted a general inhibitory effect upon the tissue, reperfusion

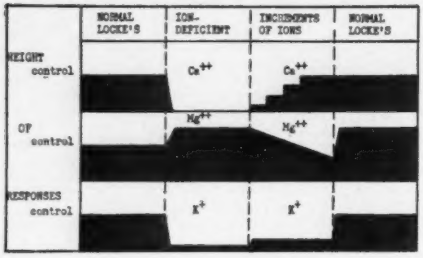

Figure 1.

with normal Locke's solution was reinstituted and repeated additions of the stimulating agents again made until no further alterations in the responses they elicited could be observed. In case a pair of ions had been removed from the Locke's solution, the effects of their addition in increasing increments first separately and then together were studied in an analogous manner. In the case of antigen, it was added to a strip at the peak of the effects observed after perfusion with deficient Locke's solution. In later experiments, it was also added at approximately the half-way mark between normal responses and the maximal effects realized by the perfusion with an ion-deficient solution.

RESULTS

Figure 1 is a diagrammatic representation of the results in experiments in which one ion had been removed from the Locke's solution; and Figure 2 is the analogous summary for experiments in which pairs of ions had been removed. In all cases the responses of the gut became altered very promptly after the perfusion with an ion-deficient solution had been inaugurated. When either magnesium or potassium was the missing ion, the initiation of the perfusion caused a sharp contraction of the gut that slowly subsided. We have no explanation for this. The maximal effect upon the responses to drugs was usually seen not long after the perfusion had been started and never more than half an hour after the start.

The removal of magnesium from the perfusion fluid augmented the responses of the gut to all stimuli. The removal of potassium ions or calcium ions much inhibited or eliminated the responses to all stimuli even though the doses of the stimuli were many fold increased (Fig. 3). The responses to electrical stimulation disappeared first, followed after variable intervals by a loss of response to acetylcholine and histamine.

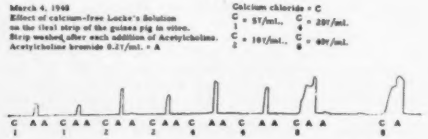
March 4, 1948
Effect of calcium-free Locke's Solution
on the ileal strip of the guinea pig in vitro.
Strip washed after each addition of Acetylcholine.
Acetylcholine bromide 0.2γ/ml. = A
Calcium chloride = C
C = 5γ/ml., C = 20γ/ml.
C = 10γ/ml., C = 40γ/ml.
G AA CAA CAA CAA C AA C AA CAA CA

Figure 4.

The responses to the last two stimuli declined pari passu.

In experiments in which calcium was the missing ion, by the addition of increments of calcium chloride

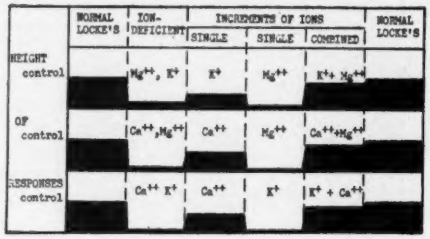

Figure 2.

to the bath, with washing after each addition and subsequent drug response, it was possible to arrange a stepwise increase in the responses as the dose of added calcium was increased, until at a concentration of about 20γ/ml., the normal control responses were again elicitable. Higher doses of calcium chloride (40-80γ/ml.) themselves caused contraction of the intestine (Figs. 4 and 5). This stepwise increase was so regular that an attempt was made to use the responses

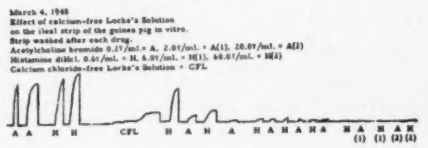
March 4, 1948
Effect of calcium-free Locke's Solution
on the ileal strip of the guinea pig in vitro.
Strip washed after each drug.
Acetylcholine bromide 0.2γ/ml. = A. 2.0γ/ml. = A(1). 20.0γ/ml. = A(2)
Histamine dihcl. 0.5γ/ml. = H. 5.0γ/ml. = H(1). 50.0γ/ml. = H(2)
Calcium chloride-free Locke's Solution = CFL
A A H H CFL H A H A HAHAHA HA HAH
(1) (1) (2) (2)

Figure 3.

as a means of quantitating the amount of calcium ions in human blood serum. The results yielded an amount of calcium ion roughly twice that known to be present in human serum, perhaps because of other stimulating substances in the serum. Responses to electrical stimulation required somewhat higher doses of calcium chloride than did those to acetylcholine.

Barium ions in a total concentration of 120γ/ml. of the chloride did not replace calcium ions nor did they interfere with the responses subsequent to the later

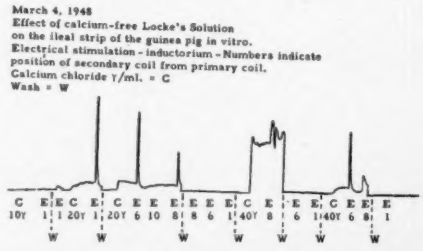
March 4, 1948
Effect of calcium-free Locke's Solution
on the ileal strip of the guinea pig in vitro.
Electrical stimulation - inductorium - Numbers indicate
position of secondary coil from primary coil.
Calcium chloride γ/ml. = C
Wash = W
G E E C E C E E E E E C E E E C E E E
10γ 1 1 20γ 1 20γ 6 10 8 8 6 1 40γ 8 6 1 40γ 6 8 1
W W W W W W W

Figure 5.

addition of calcium ions. When strontium ions were added (up to 120γ/ml. of the chloride) to replace the missing calcium ions, slight responses to the stimuli resulted. They were attributed to demonstrable amounts of calcium ion present in the strontium salt as an impurity.

In experiments in which potassium was the missing ion, it was never possible to restore the original level of responses by the addition of increments of potassium chloride to the bath. Even with the addition of potassium chloride in amounts ten times that normally present in Locke's solution, only a fraction of the control responses could be elicited. Reperfusion with normal Locke's solution, on the other hand, promptly restored the responses.

In experiments in which two ions were removed from the Locke's solution, it was never possible to restore the responses by the addition of a single ion. The addition of calcium, if it were missing, always was followed by a greater response than was seen after the addition of magnesium or potassium. Reperfusion with normal Locke's solution, however, always restored the responses.

With magnesium the missing ion, the response to added antigen seemed unaltered. With potassium the missing ion, the response to the added antigen was either slight or absent. With calcium the missing ion, no response to antigen could be elicited. If antigen were left in the bath and a suitable increment of potassium chloride added thereto, some response was obtained immediately upon the addition of the potassium chloride. Similarly if antigen were left in the bath and an increment of calcium chloride added thereto, a prompt and reasonably normal response to the antigen resulted.

DISCUSSION

Since in those experiments in which a missing ion or ions led to a loss of response to the stimuli, the response to acetylcholine and histamine disappeared pari passu, one can only conclude that they are equally dependent upon the ions concerned in their effects. It seems probable that chains of enzymatic reactions occur within the cell and that the final link in intestinal tissue is a reversible alteration in actomyosin. The speed with which the response to electrical stimulation disappeared makes it clear that this stimulus acts at a point much further removed from the final link than do acetylcholine and histamine. This supports the concept of Nachmansohn and his associates (5) that electrical stimulation does not act on the effector mechanism directly but rather acts by causing changes within the cell that lead to the formation or release of acetylcholine. For this change to be initiated the proper concentrations of potassium and calcium ions must exist in the cell. Clearly this concentration is more critical for electrical stimulation than for stimulation caused by acetylcholine and histamine.

The changes following the removal of magnesium from the perfusion fluid were in accord with the long accepted inhibitory effect of magnesium ions on the gut. The restoration of magnesium ions to the fluid never quite allowed the responses to decline to the original control level. We have no explanation for this.

Potassium and calcium ions are essential for the reversible changes in actomyosin that account for the contraction and relaxation of the muscle. They therefore act in part at least on the final link in the chain referred to above, or very close thereto. Since acetylcholine and histamine failed to act in their absence (the slight responses to high doses in the absence of potassium ions is probably attributable to a failure to wash out all potassium ions in the tissue) the focus of their attack must be further removed from the final link of the chain.

Antigen-antibody reactions would appear to cause the release of a substance that persists in the cell judging by the effect of calcium deficient solutions on these reactions. The addition of the antigen in the absence of calcium ions had no effect but the addition of a suitable concentration of calcium chloride directly to the bath led to a prompt response even though several minutes might have elapsed between the two additions.

SUMMARY

The normal responses of strips of ileum from the guinea pig to histamine, acetylcholine, electrical stimulation, and to added antigen (horse serum) were determined. A perfusion of the tissue was then initiated with a Locke's solution lacking one of three ions: potassium, calcium, or magnesium. The progressive effect of this increasing lack upon the responses to the initially tried four stimuli was then investigated. In other experiments a pair of ions was removed from the normal Locke's solution. It has been suggested that a chain of enzymatic reactions exists within the cell and terminates in the final link of the reversible change in the actomyosin molecule. Since the response to electrical stimulation was the first to disappear in the absence of potassium or calcium ions from the Locke's solution, it is suggested that this stimulus must act at a link more distant from the final link than do either histamine or acetylcholine. Since the responses to histamine and acetylcholine disappeared pari passu in the absence of either potassium or calcium, it is suggested that they have a similar focus of attack. Added antigen was without effect in the absence of calcium ions but the moment the calcium ions were added to the bath the response promptly occurred even though many minutes might have elapsed between the two additions. It is suggested on this basis that the antigen-antibody reaction leads to a release of a substance within the cell which is reasonably stable and persists for some time.

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FATAL GASTRIC HEMORRHAGE FOLLOWING AUREOMYCIN

WILLIAM P. KLEITSCH, M.D., Lincoln, Nebraska

AUREOMYCIN is enjoying a well earned popularity as an effective antibiotic for many types of infections. It is well recognized that it is only effective in acid solutions. Alkaline solutions of aureomycin deteriorate rapidly. A solution of aureomycin in water or saline solution has a pH 4.5 (1, 2). That the continuous administration of such an acid solution to a patient with a peptic ulcer might aggravate the ulceration seems to be a logical conclusion. The following case report apparently supports such an assumption.

CASE REPORT

Case No. 2. L. P., a 56-year-old white male, was admitted to the hospital on February 8, 1950, with a tentative diagnosis of cor pulmonale. He was admitted to the cardiac service and, after a thorough work-up, it was discovered that a bronchogenic carcinoma was the cause of his difficulty. In the course of the work-up, x-rays of the gastrointestinal tract were made. The impression obtained by the radiologist was as follows: "there is an ulcer present in the duodenal cap area. The cap is so deformed and so irritable that a definite niche was not demonstrated." A right pneumonectomy was done in March, 1950, from which the patient recovered rapidly, and he was discharged from the hospital two weeks later. He returned to the hospital on March 15, 1950, with symptoms of a bronchopleural fistula. He was treated by bronchoscopy and aerosol penicillin, as well as intramuscular penicillin; the fistula closed and he was discharged April 28, apparently cured. He was readmitted on July 13, 1950, again showing evidence of a bronchopleural fistula. It was discovered by bronchoscopic examination that the bronchopleural fistula had recurred. This time penicillin did not have much effect. On July 27 aureomycin was given daily in 250 mgm. doses every four hours. In spite of this, he showed little improvement and radical treatment seemed to be indicated. On August 9 a thoracotomy was done and a biopsy of thickened pleura was taken. On August 16 a Schede's thoracoplasty was done and a latissimus dorsi muscle graft was placed over the bronchopleural fistula. Aureomycin was discontinued after this last operation (after 20 days' consecutive administration) and not restarted, although intramuscular penicillin was given. His postoperative course was remarkably smooth, the temperature falling steadily toward normal. He seemed to be quite well on the way to recovery when suddenly, on the third postoperative day, he had convulsions, vomited up a pan full of blood and died within 10 minutes, despite strenuous efforts at resuscitation. A post mortem examination was done and revealed that death was caused by hemorrhage from an ulcer in the pyloric antrum immediately adjacent to the duodenum; the recurrence of the bronchopleural fistula was due to recurrent tumor. The ulcer crater was 3 cm. in diameter and 1 cm. deep. At the base of the ulcer was found a large artery 2 mm. in diameter with an ulcerated opening in its wall at least 1 mm. in diameter (Fig. 1). The artery was identified as the superior pancreaticoduodenal. The tumor in the lung was a squamous cell carcinoma, Grade III. Histopathologic examination revealed that metastases were present in the left lung, kidney, adrenals, mediastinal lymph nodes and pleura.

DISCUSSION

It is not possible to state unequivocally that the fatal hemorrhage in this case was due to aureomycin therapy. It is certain that this patient's poor general condition contributed more than a little to his rapid demise. There is no doubt that loss of appetite and a diminished intake of food, a natural result of the operations he had, would favor extension of a peptic ulceration. However, one cannot help being impressed by the fact that an ulcer crater could not be demonstrated by the radiologist in March, while five months later at autopsy a crater 3 cm. in diameter and 1 cm. deep was found. This would imply unusually rapid progress of the peptic ulcer. On the basis of this rapid progress one may be justified in assuming that aureomycin played at least a contributory role. One might well recommend that patients who receive large doses of aureomycin over a prolonged period should be carefully evaluated for the possibility of peptic ulceration. If a peptic ulcer is known to be present, it is to be strongly recommended that the ulcer be treated and that it be carefully observed by repeated x-ray examinations at four to six week intervals.

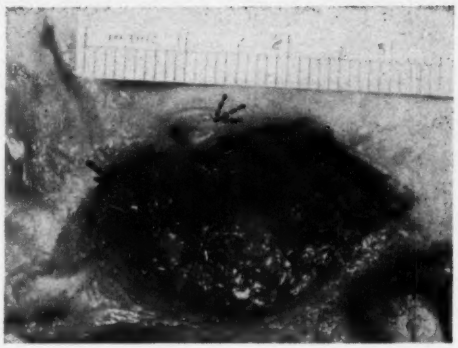

Figure 1 — A photograph of the autopsy specimen indicating the enormous size of the ulcer crater. The broken arrow indicates the open end of the divided pancreaticoduodenal artery running along the floor of the ulcer. The solid arrow indicates the site of the perforation.

SUMMARY

A fatal gastric hemorrhage is described, occurring as a result of peptic ulceration of the superior pancreaticoduodenal artery, in a patient who had received aureomycin for three weeks. The possibility of aureomycin acting as an aggravating influence on peptic ulcers is discussed. It is concluded that aureomycin should be administered with caution in the presence of peptic ulceration of the gastrointestinal tract.

From the General Surgical Service of the Veterans Administration Hospital, Lincoln, Nebraska.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are a result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Submitted October 20, 1950.

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BOWEL PERFORATION DUE TO INGESTED FOREIGN BODIES

WILLIAM P. KLEITSCH, M.D., AND G. S. SINOW, M.D., Lincoln, Nebraska

THE ORAL INGESTION of sharp pointed foreign bodies is seldom the cause of great anxiety either to the patient or to the physician. The majority are passed without producing symptoms. This is generally attributed to the fact that the pointed end of the foreign body becomes caught in the mucosa of the bowel, the object is turned about by the passage of the chyme and then proceeds innocuously through the gastrointestinal tract, blunt end foremost. Although this happy course of events is the usual procedure, perforation of the gastrointestinal tract may occur.

The following case reports describe somewhat less fortunate events subsequent to the ingestion of sharp, foreign bodies. In neither instance was the diagnosis suspected prior to surgery, since neither patient was aware of having swallowed anything unusual. It is possible that wearing dentures contributed to the inability to recognize the foreign body when it was in the mouth.

CASE REPORTS

Case No. 1. C. A. L., a 51-year-old white male, was admitted to the hospital with a tentative diagnosis of perforated peptic ulcer or bowel obstruction. Four days prior to admission he had suffered a sudden, severe, abdominal pain while he was engaged in heavy manual labor. This pain was not associated with either nausea or vomiting and normal bowel movements occurred daily. The pain, however, became increasingly severe and was the reason for his seeking hospitalization. One year prior to the present admission he had had a subtotal gastrectomy for the treatment of a perforated peptic ulcer. There had been no recurrence of his ulcer symptoms and his diet was apparently unrestricted.

Examination on admission revealed an acutely ill patient, lying quietly in bed in an effort to splint his abdomen. The abdomen was rigid and tender in all quadrants. Audible peristalsis at first was absent but was heard three hours after admission. The rectal examination was negative and a leukocytosis of 16,500 with 83 per cent neutrophils was present. The serum amylase was normal. He was observed for 24 hours, during which time he was treated with intravenous fluids, antibiotics and nasogastric suction. The next day his condition was essentially the same and a laparotomy was felt to be indicated.

At operation evidence of peritonitis was encountered as soon as the abdomen was opened. The gastroenterostomy resulting from the previous surgery was found to be intact. In the lower jejunum there was an area of serosal reaction near the mesenteric border of the bowel. No perforation of the bowel could be demonstrated but immediately adjacent to this area a sharp, pointed object was found free in the peritoneal cavity. This was removed and the area of reaction in the bowel was covered with a few interrupted sutures. More careful examination of the foreign body removed from the peritoneal cavity revealed it to be the dorsal spine of a catfish (Fig. 1). On subsequent interrogation the patient admitted having eaten catfish the day before the onset of his symptoms. The postoperative course was complicated by a wound infection which, however, responded promptly to treatment and the patient was discharged asymptomatic.

From the General Surgical Service of the Veterans Administration Hospital, Lincoln, Nebraska.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Submitted October 4, 1950.

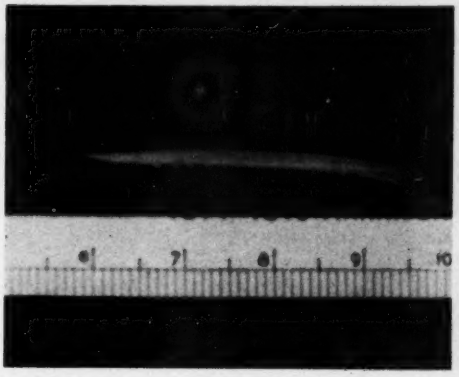

Figure 1 — The dorsal spine of a catfish found free in the peritoneal cavity after apparently working its way through the bowel wall. Note the barbs which, undoubtedly, facilitated perforation.

Case No. 2. E. J. Z., a 35-year-old white male, was admitted to the hospital for treatment of a pararectal abscess. He complained of rectal pain and tenderness coming on three days prior to admission and becoming increasingly severe. On admission the pain had localized to the right buttock and was associated with a swelling adjacent to the anus.

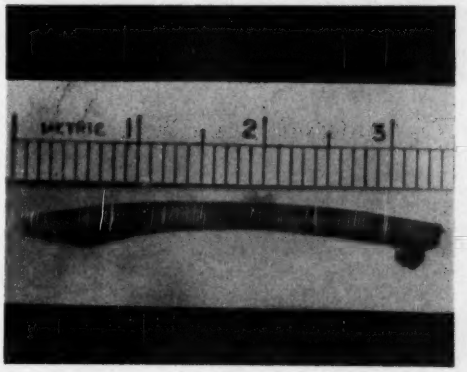

Figure 2 — A piece of bone which appears to be a portion of chicken rib found floating in an ischiorectal abscess.

Physical examination revealed an acutely ill patient, in obvious distress, with a temperature of 104°. Typical signs of an ischiorectal abscess were present on the right. He was given penicillin, sitz baths and sedation for two days until the abscess became fluctuant. He was then operated upon and the abscess was opened and drained. In this maneuver a piece of bone approximately 2.5 cm. long was found floating free in the abscess cavity. Careful search revealed no demonstrable perforation in the rectal wall. Subsequent examination

of the bone revealed it to be a piece of chicken bone (Fig. 2), apparently a piece of rib. The patient remembered eating chicken on several occasions immediately prior to hospitalization but a definite correlation between eating chicken and onset of symptoms could not be established. The postoperative course was completely uneventful.

Discussion

Although foreign bodies usually traverse the gastrointestinal tract without producing symptoms, this is not always the case. When a sharp, pointed object is known to have been swallowed, careful observation of the stool until positive assurance of its elimination is obtained is indicated. It is quite probable that the barbs on the catfish spine were responsible for its working its way completely through the bowel wall. The chicken bone passed without difficulty until the rectum was reached, where stasis and pressure of the solid feces probably contributed to forcing it through the rectal wall.

Summary

Two case reports are presented describing complete perforation of the bowel wall by orally ingested bones. Surgical treatment was necessary for each.

ABSTRACTS ON NUTRITION

Reinberg, M. H., and Lipson, M.: *The association of Laennec's cirrhosis with diabetes mellitus.* Ann. Int. Med., 33, 5, Nov. 1950.

A study of 15,450 autopsy records showed 3.7 per cent were diabetic. Of the 576 diabetics found, 5.7 per cent had Laennec's cirrhosis. In the series studied there were 5.9 per cent with Laennec's cirrhosis but without diabetes. Thus there was no significant difference between the incidence of Laennec's cirrhosis in diabetics and non-diabetics. (There were 4.7 times as many diabetics with cirrhosis and 1.5 times as many non-diabetics with cirrhosis found at autopsy as were found clinically.)

Mosenthal, H. O., and Barry, E.: *Criteria for and interpretation of normal glucose tolerance tests.* Ann. Int. Med., 33, 5, Nov. 1950.

As a result of a critical analysis of 50 glucose tolerance tests carried out on normal persons, the authors are convinced that the one-dose, two-hour glucose tolerance test, as carried out on ambulant persons and employing venous blood, gives the most reliable information. (If, in the Folin-Wu technique, Somogyi's precipitant be substituted, a true blood sugar reading results.) The criteria for normality are 100 mg. or less of glucose per 100 cc. blood in the fasting state; a maximum height of 150 mg. or less; and two hours after the ingestion of 100 grams of glucose, a level of 100 mg. or less.

Boyd, T. A. S., and Campbell, F. W.: *Influence of ascorbic acid on the healing of corneal ulcers in man.* Brit. Med. J., Nov. 18, 1950, 1145-1158.

In half of 50 cases of small acute corneal ulcer, a daily dose of 1.5 gm. of ascorbic acid was given, while the other half received control tablets. No effect was noted on superficial ulcers, but deep ulcers healed much faster on vitamin C. It was noted that pyorrhea occurred more frequently in patients with corneal ulcers than in others with non-infective eye complaints.

Lee, F. A.: *Nutritional value of frozen foods.* Nutrition Reviews, 9, 1, Jan. 1951, 1-4.

Frank A. Lee, of the New York State Agricultural Experimental Station, Cornell University, Ithaca, N. Y., states, in general, that properly processed and frozen foods not only retain their ascorbic acid content reasonably well, but constitute an increasingly significant part of the American dietary. Peas, which contain 23 mg. per 100 g. of ascorbic acid, still retain 16 mg. per 100 g. after processing and freezing. Blanching of vegetables should be done at boiling temperatures and in the shortest possible time. Rapid freezing is not essential provided the process does not require more than 12 hours. Storage is much better at 0° C. or lower. Fat rancidity and other taste defects appear where the storage temperature is above, or fluctuates above 0° C. The addition of ascorbic acid to fruits and vegetables and the ascorbic acid-dip for fish fillets gives better retention of taste and nutritional qualities.

Tomaszewski, W.: *The flourescence phenomenon of the tongue.* Brit. Med. J., Jan. 20, 1951, 117-120.

When the mouth is viewed in ultra-violet light screened with Wood's glass, a reddish-orange fluorescence usually is visible on the dorsum of the tongue and sometimes on the teeth. It is probably due to synthesis of porphyrin by microorganisms, and is found in the majority of healthy persons. The absence of the phenomenon is abnormal. A high incidence of absent fluorescence is found in pernicious anemia, hypochromic anemia, sprue syndrome and vitamin-B deficiencies. Antibiotics destroy fluorescence by their action on the microflora. The clinical significance of the phenomena is not yet known.

Brinkman, G. L.: *A survey of diabetes mellitus in Dunedin City.* New Zealand M. J., XLIX, 273, Oct. 1950.

Diabetes mellitus seems to be commoner in Dunedin than in most other cities where the incidence is known, but this may be due to a more intensive search. Twenty per cent of all patients were diagnosed by a routine urine test. Clinically the disease differs little from the commonly accepted picture.

Sherrill, J. W., and Lawrence, R.: *Insulin resistance.* U. S. Armed Forces M. J., 1, 12, Dec. 1950.

Insulin resistance is a rare clinical phenomenon, the mechanism of which is not understood. Infection aggravates the condition. In a described case, refrigeration of the gangrenous limbs preparatory to amputation brought about a dramatic fall in requirement from almost 2,000 units to less than 100 units of insulin. Following amputation and the subsidence of the effect of refrigeration, the insulin requirement promptly rose to its previous high level. Undue destruction of insulin within the body offers the most likely explanation of the phenomenon.

Joslin, E. P., and Wilson, J. L.: *Lessons for future treatment from 472 fatalities in diabetic children.* Brit. Med. J., Dec. 9, 1950.

Within the past six years, among 135 diabetic children dying, death was caused by tuberculosis in 11.2 per cent, coma in 8.8 per cent and renal disease in 51.9 per cent. Chest films should be taken annually. A constant awareness for evidences or incipient signs of renal disease must be maintained. Research should be concentrated on the kidney in the young diabetic.

Roberts, L. J.: *A practical nutrition program for Puerto Rico.* Nutrition Reviews, 8, 11, Nov. 1950.

The author, while not describing nutritional diseases as seen in Puerto Rico, recognizes the fact that the diet of the inhabitants is notably bad. Even among the eight per cent upper economic bracket, the diet, while containing better protein and more nutrients, leaves much to be desired. The typical diet in the Island consists largely of rice, beans and starchy vegetables and fruits such as green bananas, green

plantain and white sweet potatoes, and is lacking in good quality protein, calcium, riboflavine and vitamin A. The situation is due largely to low incomes but to increase incomes is difficult. The problem is being attacked by a dry skim milk campaign, education directing the greater use of yellow and green products, the raising of rabbits for food, the eating of garbanzo peas, and the enrichment of rice. Increased use of native fruits may result from the planting of fruit trees along highways for general use. The planting of vegetable gardens, and the keeping of meat and milk-producing animals also requires intensive education in Puerto Rico. The school-lunch program already serves 200,000 children in 1,500 schools. One of the encouraging features of the program is the fact that the Governor and Commissioner of Agriculture are solidly behind it.

LEIBOWITZ, H., CHESTER A., AND MARKOW, H.: *Importance of foods in patients as determined by skin testing and intentional feeding.* J. A. M. A., 144, 12, Nov. 18, 1950.

Oversimplified, the authors sought to determine how frequently symptoms of respiratory allergy would be provoked by intentionally feeding dietary articles to which the skin had reacted positively. The answer was — 35 per cent. Furthermore, in the case of dietary articles giving negative skin tests, only 1.9 per cent of them provoked symptoms when intentionally fed, which indicates that a negative skin test has great value. Wheat, milk and egg were not of etiological significance in this study either by skin test or clinical trial.

CONLEY, C. L.: *Recent developments in the treatment of anemias.* South. Med. & Surg., 112, 11, Nov. 1950.

While iron, folic acid and vitamin B_{12} are all required for normal blood formation, they should seldom be mixed together in treatment. No harm comes from oral iron but parenteral injection may prove harmful if given in too large doses over too long a time. Folic acid has few clear-cut indications. Vitamin B_{12} is all that is needed for pernicious anemia. Folic acid ought not to be used in pernicious anemia. Conley abhors present shot-gun types of preparations for treating anemia, containing, as they do, iron, folic acid and vitamin B_{12}; usually the amount of vitamin B_{12} is inadequate for oral use, while the folic acid may be sufficient to produce a temporary blood remission in pernicious anemia to be followed by a serious neurological relapse. In the past two years Conley has seen more cases than ever before of pernicious anemia with neurological manifestations in the complete absence of any blood abnormality.

STEINBERG, A. G., AND WILDER, R. M.: *A reconsideration of the phenomenon of anticipation in diabetes mellitus.* Proc. Staff Meet. Mayo Clin., 25, 23, Nov. 8, 1950.

"Anticipation" is the onset of a hereditary disease at a progressively earlier age in successive generations, presumably because of a progressive degeneration of the germ plasms. One hundred family histories in which the ages of onset of diabetes in parent and child were known were analyzed to examine the validity of the concept of anticipation in diabetes. *The analysis showed that anticipation is a statistical and not a biological phenomenon,* and hence it is suggested that the term "anticipation" be not used in discussing the observations relating to prior age of onset of diabetes in a child of a diabetic parent.

DOIG, R. K., AND WOOD, I. J.: *Gastric biopsy in pernicious anemia.* Med. J. Australia, Oct. 14, 1950, 565-568.

By means of a special instrument, the authors obtained fragments of the gastric mucosa in 33 living patients suffering from pernicious anemia, and subjected these biopsy specimens to histological examination. The extreme mucosal atrophy, which was almost invariably found, should be diagnosed as gastric atrophy, representing as it does a much more severe atrophy of glands than is observed in chronic atrophic gastritis. Patients who had received liver therapy showed no evidence of regeneration of the gastric mucosa, the condition being, in the authors' opinion, permanent and irreversible. These cases all showed considerable intestinal metaplasia of the mucosa. Almost always gastric atrophy is accompanied by pernicious anemia or subacute combined degeneration of the spinal cord. Gastric biopsy could be helpful in the diagnosis of pernicious anemia when liver therapy has been given without adequate hematological examination.

HALPER, H.: *Treatment of post-partum and menopausal obesity.* Med. J. Australia, Aug. 12, 1950, 246-248.

In treating 18 women for exogenous obesity by means of diet restriction and the administration of dextro-amphetamine sulphate, Halper obtained good results in 13, but the remaining five were considered failures because they lost less than 20 per cent of their excess weight. He found that women who became obese shortly after a pregnancy or in whom obesity occurs at, or just prior to the menopause, furnish the highest proportion of failures in treatment. Halper found that many of these women had infection of the cervix uteri and that when the infection was cleared up, their weight loss was much more satisfactory. He does not offer any explanation for this favorable effect.

EDITORIAL

WHY CANCER DEFEATS US

Many millions have been spent to control cancer, a disorder that exists each day in nearly 650,000 people in this country and causes a yearly loss of one and a half billion dollars. As a cause of death it has risen in incidence in the last fifty years from the eighth to the second cause today. Obviously this increase is not due only to better diagnoses, which would be important somewhat on the incidence, but not to much an extent on the death rate.

Man has triumphed over tuberculosis, diphtheria, pneumonia, cholera, malaria, yellow fever, and others. This is largely due to the cause having been found. Yet, there are diseases, like infantile paralysis, where the cause is known but no cure yet discovered. Unknown as to cause, diabetes, pernicious anemia, and others are, nevertheless, amenable to satisfactory treatments. Cancer, however, is still as deep a mystery as it ever was, and it is most probable that it ever will be. The electron and polarizing microscopes, x-ray defraction, centrifical analysis, radioactive isotopes, etc., have been applied to the study of the cancer cell without anything fundamental being found, and it is most probable that viruses that will restrain certain cancers in mice will not lead to finding viruses that will restrain cancers in humans. Even though certain chemical agents which produce "environmental cancer" by influencing hereditary pattern are known in the general cancer question; in humans these cannot be made to fit.

The expenditures of monies for cancer control clinics versus cancer research are two quite different affairs so far as returns or results are concerned. Cancer, as it affects human beings, is easily diagnosable in more than 80 per cent of the instances. Cancer of the skin, lips, etc., is the most common and almost obvious of easy diagnosis as is mammary, uterus, urinary bladder, cervix, and pelvic carcinomas generally, including that of the prostate. Cancer of the internal structures of the body, such as the lungs, stomach, small and large intestine, usually are suggestively disclosed by x-ray examination. Thus, there are only the minority of instances of cancer that are not diagnosable. The main matter here is that the patient does not come under observation for an examination to be made. There is no doubt that the symptomless cancer (symptomless until quite late), the temporizing person, the stubborn, and the person who just never thought of such a possibility are the majority on whom criticism can be made. On the other hand, propaganda on cancer is claimed to be foremost in responsibility for the production of cancer phobia claimed by some to be an anxiety, fearful, and worried state that does harm. What of it? Anything that inhibits a person from coming under observation is

exactly what has to be combatted, and a cancer phobia is of little significance and is easily cured by any physician. Any amount of money that is being spent in establishing and maintaining cancer clinics is a most worthy expenditure and as much interest as possible on the part of the contributing public is most worthwhile. As matters will stand for a good many years and perhaps forever, the monies should go into prevention and detection clinic funds rather than into that of research. Whatever means that will accomplish driving people to examinations is most desirable above all else, and means for this should be accessible at all times. There are modifying types of treatments but their results are trivial as compared to the great cancer question of "what is it?"

Among the significant features of the cancer process is its power of exciting the growth of new cellular connective tissue. This is an initial process of cancer production, shown in carcinomas of the prostate, breast and stomach, peritoneal metastatic growths, etc., and the bulk of connective tissue may far exceed that of the tumor cells, which really may actually disappear. This desmoplastic property of the connective tissue, so characteristic in inflammation, in cancer is, I believe, a process of immunity on the part of the tissue. In this, lymphocytes, plasma cells, capillary blood vessels and endothelium, proliferating fibroblasts with soft mucinous stroma or acellular fibrous tissue, all enter into the battle of resistance to the normal cell now situated out of place or the now designated cancer cell because it is so placed.

The cancer cell is a normal cell devoid of polarity of the epithelial cells to one another, this being due to their being free in spaces and not standing in normal arrangement of one epithelial cell with its side cells. This anaplasia increases in the disease. As the disease makes its start at a nidus, transition of the normal standing epithelium to neoplastic cells takes place, this being due to stimulating attack on free epithelial cell. This cell is most sensitive to exchanges with its environment and sensitive to stimulation of its activities, metabolic, reproductive and in stability. Further reason of the cell being a cohesive unit is that all epithelial cells have a high degree of rigidity and an ultramicroscopic or frail membrane manifestly could not give this to a cell. There is a constant reconstruction of epithelial cells in the body. These cells are dying and new ones are constantly being formed to take their place. Unless this was true, life could not be maintained. While much thought and study has been given to cell reproduction, especially the form of indirect division (karyokinesis), once the body has been formed, no studies exist or have been made on the initiation stimulus of a side cell calling for the production of a new cell to take the place of a dead one. It is not important as to how mitoses takes place, because this occurs according to a regular plan after the call for it has been made. The important matter is contained in the outside call upon a cell for reproduction, and after the synthesis has occurred, and the new cell takes the place of the destroyed one, what stops the cell from further reproduction and maintains it in static stability?

Cell division in animal tissues should be interpreted as a sexual process of which the essential act is syngamy or fusion of the two cells (gametes). Each old and new cell carries the original germ factors and these operate in the cell up to the point of protoplasmic stability or approach towards molecular equilibrium. When this occurs the cell is a fixed unit, its synthesis stopping within the cell. It then functions in a vegetative sense. Its growth has occurred, its metabolism is established, and it contains the essentials for reproduction. Each cell then contains the power for reproduction, which is manifested when one or a few cells die at the side of it. Should a row of them, or an area, die for whatever reason (traumatic, chemical, thermic effects, etc.), reproduction of the new cells would not occur, the replacement would be with white fibrous tissue. When an area destruction of the epithelium occurs, the epithelial cells make an effort to repair the loss. Either in the line of the cells or at the edges of a lesion (and lesions and efforts of regeneration of epithelial cells are occurring constantly), abnormal arrangement of connective base cells exist with perhaps openings in the connective tissue. At such points the regenerative activities of the epithelial cells are most active and such a cell gaining the interstices of the connective tissue might die, or if remaining active and regenerating would represent malignant disease. Such lesions could easily occur from inflammatory reactions from whatever cause in their efforts of repair.

The cells of carcinoma are essentially the normal cell, not running riot, but developing in locations in tissues of an organ which is not the place for them. In this way they differ from the multiplication of cells of benign tumors which mass up in a locality they originally occupied. In carcinoma, no matter how far from the original source the cell is formed, it carries with it the characteristics of the normal cell it was derived from in all of its properties of metabolism, growth and reproduction. The essential point is that malignant tumors invade the surrounding tissue and distribute throughout the body, while the cells of the benign tumors do not. It is in this distribution of epithelial cells, which are powerfully functioning cell units, that exist the main factor of malignancy. The cells of carcinoma in the lymph spaces and connective tissue originally began at the epithelial base connective tissue line (membrane propria) from a cell that was normally formed but did not achieve reproductive cell stability. In this cell the stabilizing metaplastic granules would carry along for a short time but there being no normal proximation of cells at its sides of one against the others and no longitudinal connective tissue cells at the bases of them (the essential mechanism for stabilization), stabilization could not occur. Carrying with it the sex germ factors, such a cell could develop below or further break through the supporting connective tissue cells of the normal epithelium and by further multiplication, due to the now absent inhibitory factors, it rapidly reproduces itself in the connective tissue and distributes beyond. Its rate of growth would vary greatly according to the strength of the sex factors present, the type of cell they sprang from represented mostly in their activity, age factors, etc. Once they gain the lymphatic spaces where nutrition is abundant, they multiply and spread rapidly and in some instances such cells multiply most rapidly and show giant cells of nucleated and mitotic forms. The further these cells get from their original source of origin the more rapidly they multiply, which is noted in the metastases.

At the onset of this article, the term "disorder" is used instead of "disease." Practically all diseases are due to the action of some agent. These agents may be introduced from without or may be generated within the body. The same is assumed to be the cause of cancer. But cancer pathology does not show a resisting process beyond slight connective tissue reaction. This is slight as compared to an infection or a degenerative cell process as seen in an organic disease. Cancer is a biologic phenomenon and really not a disease, as we understand diseases. The fundamental of a cancer is bound up in the sex action of the chromosomes within the cell. There is not a living cell in the body that has not within it the power of regeneration and this is transferred to the new cell that is formed. As stated before, any of these cells that get away from stabilizations or normal positions and side cell functions will in free spaces multiply and mass up into the production of a malignant neoplasm.

There are then two fundamentals: 1. The removal of all lesions that might let an epithelial cell escape into surrounding tissue, practically an impossible thing to do; and 2. having some means that would destroy the sex reproductive factors or cancer cells and none others, a totally impossible thing to accomplish. It must be obvious in the latter that here we are dealing with life itself. The laws of nature are mysterious as they are immutable and the knowledge of the physiology of the tissue, no matter how advanced, will always be short of understanding what life really is. If it were possible to have all the constituents of a normal cell in proper portions thrown together, a living cell could not be formed. There is the mysterious "touch off" that makes life and this no doubt is the function and power of the sex chromosomes which power is the initiator and the force all the way through life of the cell. This life factor is one thing that will just never be capable of analysis or understanding and is one thing that will forever be a closed book to man. The establishment of generation, the continuation of functions of the cells, and the forces that bring about regeneration are things that will always be beyond the power of man to understand. Consequently, it is my opinion, unpopular and dashing of hope as it may be, that no matter how much research is engaged in and what its character or how much money is spent on it, the cause of cancer will not become known. Surgery may be successful in removing it, and medical and other means may be found to modify it somewhat, but real prevention and cure will never be accomplished on this biologic disorder — and I hope I am wrong.

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BOOK REVIEWS

CLINICAL FACTS AND TREATMENT OF LIVER DISEASE. Etienne Chabrol, 278 pages with 58 figures. Masson et Cie, Paris, 1951.

This monograph is the third of a series of clinical and biological studies published by the author since 1941 on hepatic and biliary tract pathology. In a comprehensive review, Professor Chabrol gives his personal opinions on the three great problems which, during the past several years, have dominated the liver studies — the virus disease, cancer, and the use of antibiotics. The work deals, among other topics, with the oxidation reactions of bilirubin, the sulfophospho-vanillique reaction of serum lipids, the bacteriologic phases of contagious jaundice, the relation of infectious hepatitis to cirrhosis, the use of antibiotics and diuresis in the treatment of cirrhosis, diffuse carcinoma of the biliary tract, post-transfusion anemia rectified by RH negative blood, and the hypoglycemia of acidotic coma in bronze diabetes.

FUNDAMENTALS OF CLINICAL FLUOROSCOPY (WITH THE ESSENTIALS OF ROENTGEN INTERPRETATION). Charles B. Storch, M.D., 196 pages. Grune and Stratton, New York, 1951, $6.75.

Since this is the first book ever devoted exclusively to clinical fluoroscopy, it merits the attention of everyone doing diagnostic x-ray work, but it will prove particularly valuable — even indispensable — to the internist or general practitioner who attempts to do his own radiological investigations. It may be assumed that the x-ray specialist, being thoroughly grounded in the subject, would derive comparatively little from studying Storch's book. For others, the treatise may be relied upon to present a working-plan distinguished by its simplicity and the clarity with which it is described. The very real dangers involved in fluoroscopic work, both to the patient and the physician, are repeatedly emphasized and precautionary measures for the avoidance of over-exposure to x-ray beams and reflections are outlined. The necessity for dark-adaptation before beginning any fluoroscopic examination is made clear. The book covers examination of the chest, of the pharynx and esophagus, of the stomach and the colon. While uniformity of excellence in his teaching methods is obvious, Storch reaches a new degree of proficiency and clarity in his descriptions of cardiac examinations. The diagnosis of individual chamber enlargements is presented in such a way as to remain impressed upon the memory of the student. The book ought to be carefully studied by every clinician.

GENERAL ABSTRACTS

SELIGER, R. V.: *About alcoholism.* South. Med. & Surg., 111, 10, 306-308.

The alcoholic is unpredictable and mood-driven, and his drinking may be symptomatic of *any* major or minor reaction type. Ego weakness is the chief trouble with alcoholics — lack of independence, and feelings of inadequacy. The phantasy and escape elements also usually are present. There is not much use in psychoanalysis *alone* and neither do shock treatments *alone* help much. The patient should be approached as an individual. He needs inner peace and a return to religion. He must also be kept aware of many "don'ts" and taught to keep up his guard constantly.

HOARE, C. A.: *Amebiasis in Great Britain.* Brit. Med. J., July 29, 1950, 238-241.

Between one and four million of the inhabitants of the British Isles are infected with *E. histolytica*, almost all of them being merely "carriers" without evidence of tissue invasion. It is believed that the parasite usually lives a purely commensal existence in the lumen of the gut. There may be a large strain and a small strain of *E. histolytica*, the former alone being capable of producing amebiasis. Clinical cases of the disease in England may possibly be entirely due to imported virulent strains. The presence of so many carriers presents a public health problem, and betrays that individual and communal hygiene is imperfect. There is not much use in trying to free carriers of the parasite.

VAICHULIS, J. A., LITTMAN, A., IVY, A. C., ZUBOWICZ, G., AND KAPLAN, R.: *The chronic typhoid carrier. III. Therapy with antagonistic bacillus, antibiotics and sulfonamides.* Ann. Int. Med., 33, 2, 361-370.

In intestinal carriers of typhoid, the authors met with success in rendering them non-carriers by one, or both, of two methods. The first method was the feeding of watery suspensions of a typhoid-inhibiting gram-positive, spore-bearing organism, resembling *B. subtilis.* The second method consisted of massive doses of penicillin in combination with carinamide (a mixture of three sulfonamides) and tetraiodophenolphthalein. If gall stones are present, cholecystectomy should be done. If the gall bladder is visualized (without stones) medical treatment is likely to succeed. If the gall bladder is not visualized, it probably will need to be removed before treatment will prove successful. The subject of urinary carriers will be considered later.

HOLLOWAY, J. B., AND CUMMINGS, M.: *An evaluation of a method of obtaining gastric washings.* Am. Rev. Tuberculosis, August 1949, Vol. 61, No. 2, 228-235.

In a search for tubercle bacilli in gastric washings the size of the tube used is of no importance but the shorter the time interval between collection and culture, the greater the chance of success. Smears made from gastric contents are unreliable whether found positive or negative. A greater number of positive cases will be found if repeated gastric washings are used. Cultures should be made immediately of each gastric lavage and the contents of several ought not to be combined as one. Both guinea pig inoculation and cultures should be used in the search for the tubercle bacillus in gastric washings. Of 53 consecutive patients whose sputum had been previously negative for the bacillus, the repeated gastric washings finally revealed the bacillus in 22.

SCOTT, R. B.: *The spleen and splenectomy.* Brit. Med. J., June 18, 1949, 1063-1070.

Rupture of the spleen and thrombosis of the splenic vein are, of course, indications for splenectomy. Apart from these two conditions, the indication for the operation is an imbalance of the delicately poised equilibrium between the hematopoietic functions of the bone marrow and the inhibitory and hemolytic activities of the spleen. This may arise from a primary splenic disorder or be secondary to many forms of splenomegaly: it may be due to hypoplasia of the bone marrow or to the production of malformed red blood cells; it may affect the erythrocytes, the granular cells, or the platelets, severally or concurrently. In every variety splenectomy may restore the blood to normal and the patient to health.

CHAMBERLIN, C. T.: *Hemochromatosis: report of a case in a white female without diabetes.* J. Arkansas Med. Soc., July 1949, Vol. XLVI, No. 2, 45 50.

The case reported is interesting because thus far, after 12 years of observation, diabetes has not developed. Only gradually did the brownish discoloration of the skin develop and deepen. Skin biopsies at first revealed increased melanin

but no hemosiderin, but recently crystals of the latter were discovered. The patient usually carries a mild simple anemia, has bouts of indigestion and abdominal pain, and suffers most from general pruritus. It was accidentally discovered that intramuscular injections of penicillin, either crystalline or procaine, were effective in controlling the itching. She had a thyroid resection for adenoma. The disease usually attacks males and is considered to be due to an inborn error in iron metabolism.

GASKELL, H. S.: *Treatment of herpes zoster with liver extract.* Brit. Med. J., June 11, 1949, 1037.

In 20 cases of painful herpes in various parts of the body the author obtained what appeared to be remarkable and very quick results both on the pain and the evolution of the lesion in 18, by the daily injection intramuscularly of from two to four cc. of liver extract. As a rule only two or three injections were required to make the patient comfortable.

BINTER, P. A., AND RANKIN, T. J.: *The relief of peptic ulcer pain by tetra-ethyl-ammonium chloride.* Ann. Int. Med., 33, 3, Sept. 1950, 649-658.

Tetraethyl ammonium chloride (T.A.C.) when administered intramuscularly produces a transient pharmacologic blockage of the vagus with halting of gastric motility. In dosages of 500 mg., T.A.C. consistently relieved the severe pain of peptic ulcer in all 27 patients receiving the treatment. From further experience the author, in cases where pain is not relieved or incompletely relieved, has learned to suspect the following reasons,—penetration with local peritoneal irritation, organic pyloric obstruction, or marked exaggeration of symptoms of psychic origin. Further trial of T.A.C. is warranted in peptic ulcer. Side effects included blurring of vision, lowering of blood pressure, absence of perspiration and pain at the injection site.

BEAN, L. L. AND STONESTREET, M. P.: *Vagus resection.* U. S. Armed Forces M. J., 1, 9, Sept. 1950, 985-995.

19 cases of vagus resection were studied and the value of this operation in causing relief of ulcer pain is emphasized, also its appropriateness in marginal ulcer or in cases where other types of surgery have failed. Pyloric obstruction if present should be surgically relieved, and it ought not to be forgotten that no form of surgery can relieve the underlying psychosomatic condition that is present in many ulcer cases.

HOSFORD, J.: *Some aspects of partial gastrectomy.* Brit. Med. J., May 28, 1949, 929-932.

Two hundred cases of partial gastrectomy for peptic ulcer are reviewed with particular attention to the causes of postoperative mortality. The peritoneal cavity ought to be drained following the operation. Antecolic and retrocolic anastomoses are apparently equally good. There is little practical evidence that a valve at the anastomosis makes much difference to the symptomatic result, except possibly by decreasing the liability to bile regurgitation.

KUHNS, D. M. AND WETHERBEE, D. G.: *An epidemic of vomiting and diarrhea.* U. S. Armed Forces M. J., 1, 8, 861-865.

In the fall and winter of 1948, epidemics of acute gastroenteritis occurred in the San Antonio area, characterized by sudden onset of nausea, vomiting and diarrhea and accompanied by low fever. The disease subsided in from 24 to 72 hours and was not associated with any respiratory symptoms. Laboratory studies failed to reveal the etiological agent, but a viral origin was suspected.

LAWLER, A. L. AND HIRST, R. R.: *The hanger cephalin cholesterol flocculation test and the Maclagan thymol turbidity test.* U. S. Armed Forces M. J., 1, 8, 902-912.

122 autopsy diagnoses of liver disease were correlated with the thymol turbidity and cephalin cholesterol flocculation tests and found to be in accord with the clinical results reported in the literature. The thymol test was twice as reliable as the cephalin test. Possibly the thymol test is an index of liver regeneration.

PERRY, B. F. AND ZUSKA, J. J.: *Syndrome of circumoral pigmentation associated with generalized intestinal polyposis.* U. S. Armed Forces M. J., 1, 7, 773-777.

The authors refer to a well-substantiated syndrome in which polyposis of the small and large intestine is found in persons having black pigmentation of the lower lip, sometimes also of the skin near the mouth, the upper lip and the buccal surfaces. A case of small and large bowel polyposis is described in a boy who had marked pigmentation of the lower lip. This is probably a sporadic instance of a syndrome usually clearly hereditary and transmitted as a simple mendelian dominant. When such pigmentation is seen, polyposis should be suspected and searched for, particularly if abdominal colic or obstruction is present.

GASTER, J.: *The surgical importance of internal hernia.* Alex. Blain Hosp. Bull., Feb. 1949, Vol. 8, No. 1, 1-13.

The author shows that internal hernias may be asymptomatic, and are occasionally incidental findings while operating for other conditions. Intestinal obstruction due to internal hernia, even in the absence of strangulation, carries a high mortality rate simply because the diagnosis usually is not considered. The importance of a familiarity with the various types of internal hernias is obvious, and the author adds another group to the standard classifications, viz., hernias through defects in the falciform ligament. The diagnosis may be made before operation if the condition is kept in mind.

CONWAY, M. E.: *Intussusception of the appendix.* Ill. Med. J., June 1949, Vol. 95, No. 6, 370.

A boy of 5 developed indications of appendicitis and a W. B. C. of about 30,000. At operation the appendix was found to have intussuscepted into the cecum. Histologically the appendix was normal. Recovery was uneventful.

DEWAR, M. R.: *The saliva: a short review, with special reference to dental caries.* Med. J. Australia, June 17, 1950, 803-806.

A study of saliva (a secretion which has been notably neglected by scientists) has been partially fruitful in that some direct correlation between the lactobacillus counts and dental caries has been established. The lactobacillus counts were lessened in individuals using a lowered carbohydrate diet, and among such persons there was a decreased incidence and progression of tooth decay. The author feels that the addition of certain substances to tooth-pastes may be of great importance in retarding dental caries, although the final answer is not yet available. The fluorine ion, vitamin K, indole, iodoacetic acid and ammonium phosphate have all proved moderately effective.

JONES, C. M.: *The evolution and treatment of late disease of the liver.* Ann. Int. Med., 33, 2, 292-297.

The tendency of the liver to regenerate after injury to, or destruction of its parenchyma, makes certain disease processes reversible under some circumstances, but the process of regeneration usually is disorderly and newly formed masses of liver tissue, by pressure on the portal veins, may lead to fatal, portal hypertension. In treating liver disease, rest is of paramount importance in order to avoid excessive metabolic requirements. A diet rich in protein and in calories is equally important and represents a *sine quo non* of recovery. Ascites may be reversible and is not, in itself, a sign of hopelessness. The esophagus should be examined for varices, for their appearance is of poor prognostic significance. In selected cases, reduction of portal hypertension by spleno-renal or porto-caval shunt is life prolonging.

ASHE, W. M. AND SEYBOLD, W. D.: *Congenital atresia of the esophagus with tracheo-esophageal fistula treated by primary esophageal anastomosis: report of 8 cases.* Proc. Staff Meet. Mayo Clin., June 8, 1949, Vol. 24, No. 12, 327.

Prompt diagnosis is urgent because atresia is incompatible with life and good surgical correction usually possible. The chief symptom is dysphagia. Pneumonia and dehydration must be combatted before and after the operation. The trachea-esophageal fistula is closed and an end-to-end anastomosis done between the two ends of the esophagus. The approach was through the right posterior portion of

the thorax in an extra-pleural plane. Adequate fluid intake post-operatively is best assured by doing a temporary gastrostomy. Antibiotics and sulfonamides are usually advisable. The results are gratifying.

WANGENSTEEN, O. H.: *Diagnostic and therapeutic considerations in management of the acute abdomen.* Northwest Med., May 1949, Vol. 48, No. 5, 315-318.

In perforating injuries, the abdomen should be opened, and in blunt injuries great caution is necessary should operation be at all delayed. Surgical treatment of acute appendicitis, perforated ulcer and simple bowel obstruction has greatly improved in the past decade. We must now try to evolve methods of reducing the mortality from ulcer hemorrhage. Obstruction due to strangulation still presents a real therapeutic problem. Indwelling duodenal tubes have been helpful in simple obstruction but if the presence of a strangulation is not recognized it is obvious that early recourse to surgery is passed up, and the life of the patient is likely to be sacrificed.

JENKINSON, E. L., PFISTERER, W. H. AND SEITZ, E. P.: *Primary tumors of the small intestine.* Radiology, 55, 1, 12-19.

At St. Luke's Hospital, Chicago, from 1938 to 1948, 16 cases of small intestinal tumors were found during operation, of which 12 were malignant and 4 benign. Seven were located in the duodenum, 2 in the jejunum and 5 in the ileum. The most common symptoms were obstruction and melena. Although x-ray examination is the most important diagnostic procedure, it has not as yet reached the efficiency it has attained in the diagnosis of gastric and colonic lesions.

BELL, J. C.: *General considerations in the roentgen examination of the colon.* Radiology, 55, 1, 20-23.

Bell advises caution, patience, hard work, and repetition, since the proper x-ray examination of the colon is very difficult. Castor oil is a good cleaning agent. Gentle manipulation and slow injection combined with reassurance to the patient are necessary. Double contrast media will be needed in 10 percent of cases of suspected polyps.

GIANTURCO, C.: *High-voltage technic in the diagnosis of polypoid growths of the colon.* Radiology, 55, 1, 27-29.

The author uses one part of barium powder to four parts of water by volume and then voltage high enough to penetrate this mixture. He uses 100 kv., 300 ma., ¼ to ⅓ sec., Bucky, 36 inches distance, par speed screen, obtaining soft gray instead of the black and white films which show so little of the inside of the colon. By employing three 14x17 films, one supine left oblique centered to show the rectum and sigmoid, one supine right oblique, and one prone, it can be shown that the shadow of a true polyp remains unchanged in the various views, whereas fecal material or air shifts.

COLEMAN, P. N.: *Anomalous findings in differential diagnosis of jaundice by biochemical tests.* Brit. Med. J., July 29, 1950, 246-248.

Maclagan showed that by using simply the estimation of serum alkaline phosphatase and his thymol turbidity test, it was usually possible to distinguish between hepatocellular and obstructive jaundice. In 200 cases examined he found no exception to this rule: a low alkaline phosphatase (less than 15 units) or a strongly positive thymol turbidity reaction (greater than 8 units), or both, indicate that the jaundice is non-obstructive, while reversed findings indicate obstruction. Coleman, in a series of 46 cases, found 4 instances where Maclagan's tests gave anomalous results. Coleman seemed to get better diagnostic indications from detecting excess urobilinogen in the urine and derangement of the albumin: globulin ratio of serum protein.

OGILVIE, A. G. AND SPENCER, I. O. B.: *Hemorrhage from peptic ulcer.* A report on 170 cases. Brit. Med. J., July 15, 1950, 138-141.

A series of 170 cases of hemorrhage from peptic ulcer with an overall mortality of 2.4 percent is reported. The bleeding patient was given morphine on admission and then 6 ounce milk feedings every 2 hours, and other fluids forced per os. Magnesium trisilicate is given only if the patient complains of pain. 500 mgm. of ascorbic acid are given daily. Iron is used at a later stage to combat anemia. Blood transfusions were given when required as determined by hourly pulse rates and personal assessment of the patient's condition. Only 4 deaths occurred in the series. Only two cases were treated surgically because of bleeding and one of these died. The authors believe the good results justify the idea that bleeding ulcer is best treated medically. Seventy-one of the patients were 50 years of age or older. Only 27 were over 60. Three of those who died were over 50, two being in their seventies. The comparative youthfulness of the series (143 under 60) may have been a factor in the good results obtained by medical treatment.

SCHINDLER, R., SCHLOSBERG, S. S. AND BENJAMIN, M.: *Radiation therapy of carcinoma of the cardia.* Radiology, 55, 2, 223-227).

In 3 patients with clinical carcinoma of the cardia, the tumor reacted favorably to deep x-ray. One case was verified at autopsy, and one by two laparotomies and autopsy. In these two cases the tumors within the stomach had disappeared except for minimal microscopic residues. Metastases led to the fatal end. Distress was relieved and life prolonged. It is easy to reach a tumor of the fixed cardia with the proper amount of radiation. If the tumor involves mobile portions of the stomach, its position should be determined, prior to each irradiation, by fluoroscopy after the ingestion of a small amount of barium, with the patient in the position to be used at that treatment.

BACON, H. E. AND MORAN, T. F.: *Management of hemorrhoids.* G. P., 11, 2, 59-60.

No one should operate on the rectum unless he has had experience. No operation for piles should be undertaken until more serious disease in the rectum and colon has been ruled out. The injection treatment of internal hemorrhoids is an adequate means of therapy, but only in selected cases. It is indicated only when piles of the internal variety are small, of moderate size and uncomplicated. For permanent cure, a well-executed surgical removal of the hemorrhoids is the best procedure. Low lumbar block anethesia gives the best relaxation. Sharp dissection of the hemorrhoidal excrescences, accurate approximation of the mucosal edges with fine catgut, the omission of all packs and plugs, early ambulation, and hot Sitz baths with periodic inspection of the wound are recommended.

THOREK, P.: *The acute abdomen.* J. Indiana State Med. Assn., 43, 8, 745-750).

Confusion in diagnosis of the acute abdomen arises chiefly from difficulty in differentiating among 6 conditions,—acute appendicitis, acute cholecystitis, perforated peptic ulcer, acute hemorrhagic pancreatitis, renal colic, and coronary disease.

The most common symptom in acute appendicitis is anorexia, and if the patient states his appetite is not altered, Thorek doubts the diagnosis of acute appendix. A high polymorphonuclear percentage associated with a low white blood count means a poor prognosis.

Pregnancy is a predisposing factor to acute cholecystitis because it is associated with a physiological hypercholesterolemia and the lipid, becoming deposited on the mucous membrane of the gallbladder, forms polypi which break off and become the nuclei for stones. The patient is "fair, fat, fertile, flatulent, flabby and a female of forty" (7 "F's").

The silent abdomen is important in the diagnosis of perforated ulcer. Patients with pancreatic disease usually are found lying on the abdomen or in a sitting position.

In renal colic, a zone of hyperesthesia is found posteriorly at the level of and slightly below the twelfth rib. If this area is anesthetized with novocaine, the hyperesthesia and pain disappear. When abdominal pain is due to coronary thrombosis, no area of local abdominal tenderness is ever found.

LAZARUS, S. S., SACKLER, M. D., SACKLER, A. M., SACKLER, R. R. AND CO., TUI: *Fasting achlorhydria and hypochlorydria, produced by protein hydrolysate therapy of peptic ulcer.* Rev. Gastroent., 17, 8, 669-674.

The long term effect of substitution of protein hydrolysate and dexin for the normal diet in peptic ulcer patients is a marked reduction of fasting gastric acidity. This reduction in fasting acidity may be adrenal-cortex-mediated response

based on increase in the adaptive mechanism as a result of prolonged hyperproteinization.

SAVAGE, T. AND STITCHBURY, P. C.: *Spontaneous rupture of the esophagus.* New Zealand M. J., XLIX, 271, 276-277.

A woman of 57 vomited without warning and at once noted pain in right lower chest; dyspnea and collapse resulted. Infected food material was aspirated from the right chest, and the latter surgically drained. She died 33 hours after the first symptoms. Autopsy revealed a spontaneous 3 inch tear in the esophagus, which probably resulted from violent vomiting. Her poor condition prevented repair of the ruptured organ.

JOSLIN, E. P. AND RISLEY, T. S.: *Gastroenterological conditions and complications in the course of diabetes mellitus.* Rev. Gastroent., 17, 8, 643-648.

Joslin emphasizes that in diabetics the symptoms of acute appendicitis are very mild and this applies to symptoms of peptic ulcer as well. Could this mildness of symptoms be due to a coexisting neuropathy in some cases? Pseudoperitonitis due to dehydration is puzzling and has led to needless operations. Surgery on the diabetic must be of highest quality, since the patient is always a substandard risk.

MCGOWAN, J. M.: *Complications and sequelae of gall bladder disease.* Rev. Gastroent., 17, 8, 649-654.

The diseased gall bladder is capable of producing pancreatic edema, duodenal spasm, cholangitis, gastritis and even cardiac disease. Paroxysmal tachycardia is frequently associated with gall bladder disease and even coronary thrombosis may be precipitated by gall bladder disease. McGowan believes that arthritis associated with gall bladder is due to impaired nutrition resulting from disturbances of digestion.

HALBRECHT, I. AND BRZOZA, H.: *Evaluation of hepatic function in newborn infants by means of chemical study of cord blood.* Am. J. Dis. Child., 79, 6, 988-995.

The serums of the cord blood of 74 newborn, premature, full term and hypermature infants and the venous blood serums of 10 mothers and 10 infants on the 8th day of life was used. In 68 of the 74 newborn infants a protein level of less than 6 Gm. per 100 c. c. of serum was found. The average albumin-globulin ratio was 2.52 in the premature infants, 1.61 in the full term and 1.62 in the hypermature. Figures and results also are given for bilirubin concentration, van den Bergh reaction, cholesterol value (100.3 mg.) cephalin flocculation reaction (positive in 64), thymol turbidity test, Takata-Ara test, cadmium flocculation, and the Weltman coagulation band shift.

BRINDLEY, G. V. AND WHITE, R. R.: *Carcinoma of the colon and rectum.* Texas State J. M., 46, 8, 599-601).

After a review of 554 cases of cancer of the colon and rectum seen from 1918 to 1943, the authors conclude that the size of lesion, the site of the lesion in the colon, the patient's statement as to the duration of symptoms before resection, the presence of obstruction, and the age of the patient *per se* have little influence on the prognosis. Rather, the most important factors in the cure of colonic cancer and rectal cancer are,—the early diagnosis, the grade of the lesion, the extent of the growth, and the nature of operative procedure, which should be prompted by an aggressive and radical surgical approach.

OWEN, J. G. AND STONE, C. S.: *Treatment of peritoneal adhesions.* Bull. Mason Clin. IV, II, 50-56.

A report is given on 39 cases of peritoneal adhesions. Multiple previous operations increase the likelihood of adhesions and resulting obstruction. Talcum powder granulomata were found in two cases. In simple, single-band adhesions, severance of the band with peritonization of the raw surface is adequate for permanent relief. The operation of choice in extensive matting and kinking of the bowel by adhesions is careful separation of the loops, and serial plication of the folded loops, closing the adjacent edges of the mesentery leaves. In hopelessly snarled bowel, not involving too extensive an area of gut, resection is desirable, or sometimes partial exclusion by short-circuiting side-to-side anastomosis.

HUZELRIGG, T. R. AND BAKER, J. W.: *Gallstones not palpable at operation: a case report.* Bull. Mason Clin., IV, II, 42-45.

A 43-year-old woman had several small gallstones in her gallbladder in spite of the following facts, (1) repeated x-ray examination of the gallbladder showed good function and no indication of stones, (2) palpation of the gallbladder at laparotomy did not suggest stone until the organ was emptied, at which time the presence of stone was confirmed by palpation. The case was further confused by the x-ray finding of a duodenal ulcer which at operation was found to be healed. Her history of repeated severe attacks of pain characteristic of gallstone colic constituted the chief diagnostic anchor and caused the surgeon to persist in his efforts to demonstrate stones. The authors point out that, in this age of refined diagnostic techniques, we ought to rely chiefly upon the history and physical findings.

DR. RUSK RECEIVES 1951 RESEARCH AWARD

A.P.M.A. Honors Him For Work In New "Third Phase of Medical Care"

Boca Raton, Fla., April 3—The annual Research Award of the American Pharmaceutical Manufacturers Association, two of whose four previous winners subsequently won the Nobel Prize in Medicine, was presented here today for the first time to a clinician. He is Dr. Howard A. Rusk, director of the Institute of Rehabilitation and Physical Medicine of the New York University-Bellevue Medical Center, and associate editor of *The New York Times.*

Dr. Rusk's contribution to the development of the "third phase of medical care" was the basis of the award, according to Dr. Martin Lasersohn, vice-president of Winthrop-Stearns Inc. and chairman of the association's research board, which made the presentation at the opening of the 44th annual session in the Boca Raton Club.

Now recognized as an essential phase of medicine and a socio-economic problem, the "third phase" is devoted to the care of the handicapped from the time they leave their beds until they are satisfactorily employed.

The A.P.M.A. award was established in 1947. It is made "in recognition of the work of an investigator who has made a significant contribution in the field of medicine or the medical sciences."

Previous winners were Dr. Bernardo Alberto Houssay of Argentina; Dr. Dilworth Wayne Woolley of the Rockefeller Foundation; Dr. Selman Waksman of Rutgers University; and Dr. Edward C. Kendall of the Mayo Clinic, discoverer of cortisone. Dr. Kendall and Dr. Houssay received the Nobel Prize.

"Dr. Rusk's research has directly affected the lives of many thousands of service men and civilians," Dr. Lasersohn said in his address. "His own clinical management of patients has rehabilitated to active useful life innumerable individuals who have sustained catastrophic accidental injury or who have become crippled from such paralyzing conditions as poliomyelitis, multiple sclerosis, cerebral palsy, paraplegic and viral spinal cord infections."

While in the military service during the last war, Dr. Rusk was Chief of the Convalescent Services Division of the Army Air Forces. He then first brought into prominence the "third phase" of medical care." Awarded the Distinguished Service Medal in 1945, he now holds the rank of brigadier general in the reserve.

"Since the end of the war, Dr. Rusk has with great vigor and expertness attacked the problem of the disabled civilian," Dr. Lasersohn continued. "He has pointed out that World War I produced about 400 paraplegics, only one of whom is alive today. World War II resulted in 2,500 paraplegics, and eighty per cent of these are now living useful lives. Dr. Rusk's personal experience with his 130 paraplegic miners bears out further what can be done for these so-called hopeless cases. One hundred of the miners treated by him were capable of following a program of continued vocational training or were able to return to some gainful work in the mining industry."

The Institute, built largely through the efforts of Dr. Rusk, provides a well integrated program of physical therapy, occupational therapy, physical rehabilitation, social service, vocational guidance and recreation, Dr. Lasersohn pointed out. Specially built, it contains the most recently developed equipment. Rehabilitated handicapped personnel compose most of the Institute's teaching and maintenance staff.

"A dozen or more research projects are going on all the time," Dr. Lasersohn said. "They are studying the gait patterns in types of neurologic conditions, especially in hemiplegia, the one-sided paralysis that results from apoplexy. They are working on what the general practitioner should do with his multiple sclerosis cases, trying to develop a program which can be set up at home for the handicapped.

"The Institute is also studying ways of simplifying housework activities, to bring benefit to housewives suffering from damaged hearts and handicapped in energy expenditure. Research is being conducted with several substances which may possess spinal cord regeneration effects.

"Such fundamental research in physical medicine will undoubtedly lead to great practical benefits for the nation's handicapped. For devoting himself to a phase of medicine and a social enigma once dismally neglected, a phase where in the past many patients lay or sat immobilized, leading a vegetative existence, the Board presents its annual award to Dr. Rusk."

TINLESS CAN PROJECT CITES AS PERMANENT, NOT STOPGAP, EFFORT

Scientific research for a completely tinless can seeks to free permanently this continent from dependence on foreign sources of can-making materials—not just to tide the industry over in times of shortages and high prices of these materials, W. C. Stolk, executive vice president of the American Can Company, stated today.

"Regardless of what happens to the price and availability of foreign-produced can-making materials following the present emergency," Mr. Stolk added, "we will continue to push our research for a container that will match or better the present tin can in serviceability and economy and that can be made entirely from materials available on this continent."

He referred to American Can's research program—called "Operation Survival"—which has been actively under way for the past two years in conjunction with more than 20 leading American companies which are potential suppliers of alternate can-making materials.

Citing the recurrence of the threat to Far East tin sources and the high prices in world tin markets, the container company executive declared the time has come to "free the industry, can users and the public permanently from the uncertainties and disruptions that, in times like these, are inherent in dependence on foreign sources of tin and other container materials."

He pointed to the development during World War II of electrolytic plate for can manufacturing as part of an emergency conservation program that saved 90,000 tons of tin. While this was a war-time measure, he added, "the practicality of this plate was so well demonstrated it has remained in widespread use ever since."

Mr. Stolk said that on the basis of findings to date of his company's research program a tinless can for every packaging purpose is now a foreseeable development.

CITIZENS COMMITTEE FOR THE HOOVER REPORT

New York, April 9.—The formation of a nation-wide committee of doctors to support the recommendations of the bipartisan Hoover Commission in the field of health was announced today by Dr. Robert L. Johnson, president of Temple University and national chairman of the Citizens Committee for the Hoover Report.

Dr. Robert Collier Page, general medical director of Standard Oil Co. (New Jersey), was chosen at an organization meeting here today as chairman. He will begin immediately the formation of his committee of specialists and general practitioners which is expected to number several thousand members in all parts of the country.

The National Doctors Committee will have two major objectives: (a) to work for the conservation and fullest use of the nation's supply of trained doctors, nurses and technicians and, (b) the coordination of federal hospital facilities through a Federal Department of Health, as recommended by the bipartisan Hoover Commission.

Divisional chairmen will be appointed for each of the major branches of medicine and an advisory board of 20 doctors will consult with the national chairman on matters of policy. Educational material will be supplied by the Citizens Committee for the Hoover Report. It will be designed to inform doctors of the country of the conditions in the field of health disclosed by the survey made by the Hoover Commission.

To avoid misunderstanding of the aims of the committee, Dr. Page made this comment:

"A federal Department of Health will not mean 'socialized medicine' and it will not be 'just another government agency.' It will unite the facilities and resources of existing agencies; it will add efficiency, responsibility, singleness of operation and economy—in men, skills, and money."

It is expected that the committee will be active during Congressional consideration of the bills for the creation of a United Medical Administration recently introduced in Congress. Prominent doctors are ready to testify before Congressional committees considering these measures.

Dr. Page joined Jersey Standard in 1939, and in 1946 became the coordinating head of its medical organization, the largest of its kind in the world. During World War II, he was a Flight Surgeon and later Command Surgeon for the First Air Commando Force which took part in the first air invasion of Burma. Before his discharge from military service with the rank of Lieutenant-Colonel, Dr. Page served as Chief of Professional Services for the Personnel Distribution Command.

Dr. Page was graduated from the University of Detroit in 1930, and received his medical degree from Northwestern University Medical School in 1935.

He is a Diplomate of the American Board of Internal Medicine, Fellow of the American College of Physicians, member of the New York Academy of Medicine, director of the American Association of Industrial Physicians and Surgeons. He is head of the Scientific Session of the 1951 medical conference of that group to be held this month at Atlantic City. Dr. Page is an As-

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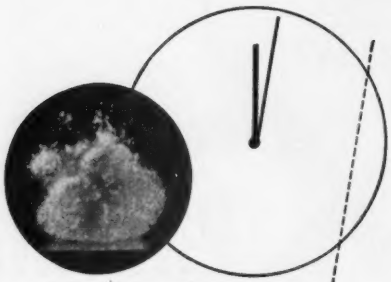

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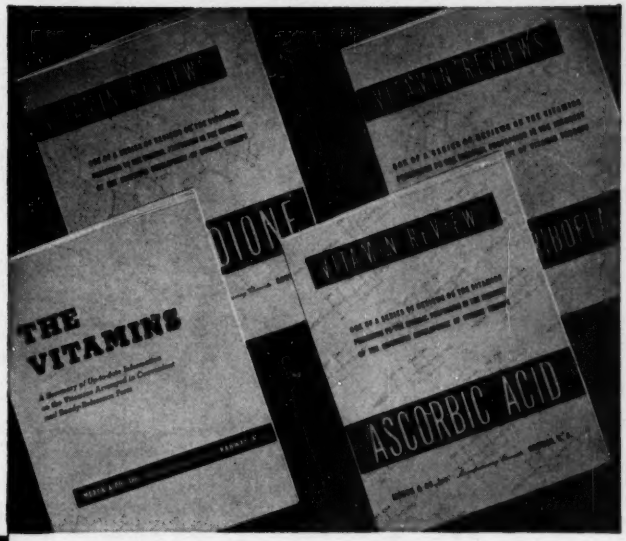

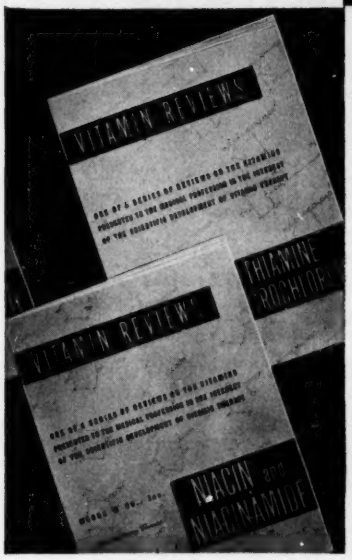

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- Distribution in foods.
- Methods of administration.
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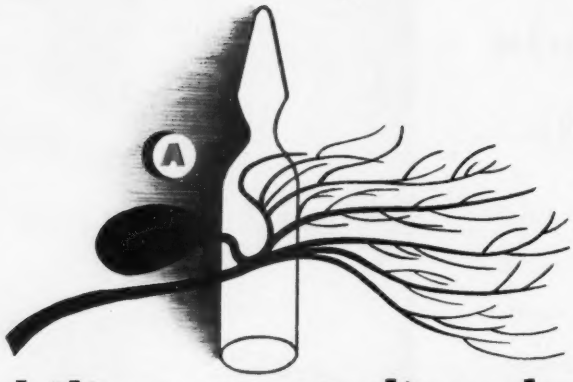

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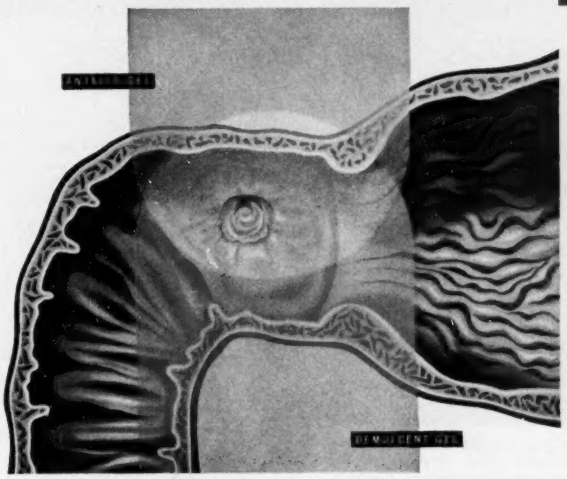

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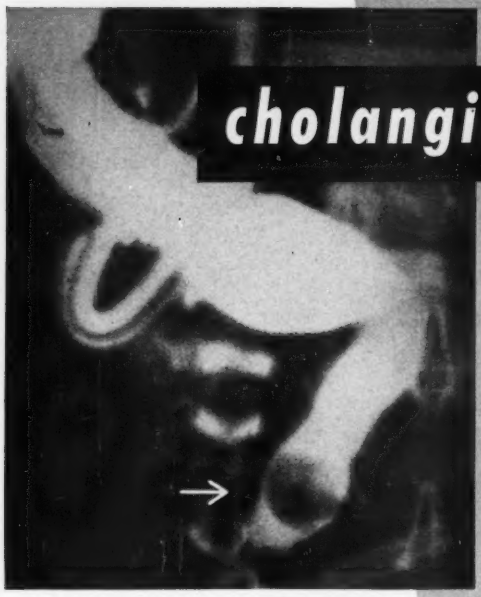

cholangiography

Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

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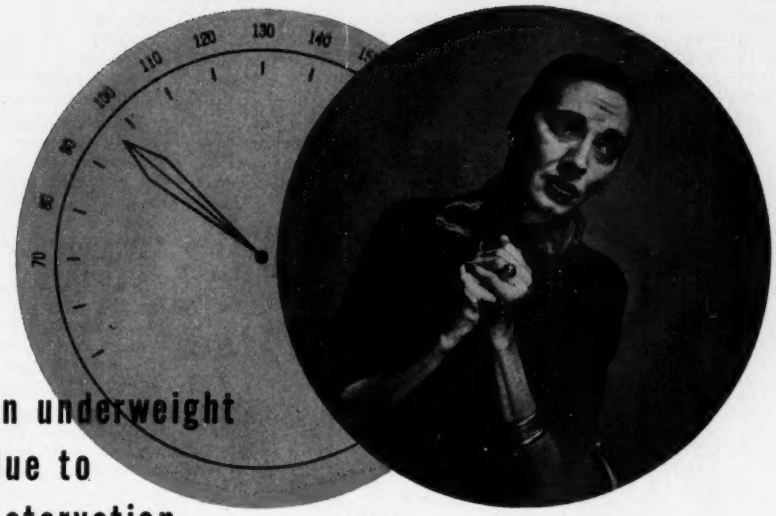
1. Byrne, R. V.: *Amer. Jour. Surg.*, 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: *Amer. Jour. Surg.*, 78:347, Sept., 1949.



when underweight is due to fat starvation . . .

. . . as frequently occurs in the young and aged[1], or in sprue, celiac disease, pancreatic fibrosis, ileitis, or following gastric surgery[2,3], — extraordinary measures must be taken to insure absorption and utilization of this vital nutrient so intimately connected with many metabolic activities, particularly fat-soluble vitamin utilization.

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Ref.:

1. Becker, G.H., et al.: Gastroenterology 14:80, 1950
2. Jones, C.M., et al.: Ann. Int. Med. 29:1, 1948
3. Jones, C.M.: Cal. Med. 71:253, 1949
4. Kiefer, E.D. & Arnold, W.T.: J.A.M.A. 144:903 (Mar. 11) 1950

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sociate Clinical Professor of Industrial Medicine at New York University and is on the medical staffs of the University Hospital and the New York Hospital.

SULFAMYLON FOUND TO KILL GERM CAUSING EAR INFECTION

One of the newest sulfa drugs, sulfamylon, has been found effective in destroying the organism believed responsible for otitis externa, the now common ear infection that involves inflammation of the opening, scaling and itching.

A simple method which achieves "uniformly good results" in treating the infection is reported in *Laryngoscope* by Dr. J. W. McLaurin of the Tulane School of Medicine. The patient himself plays an important role in the treatment.

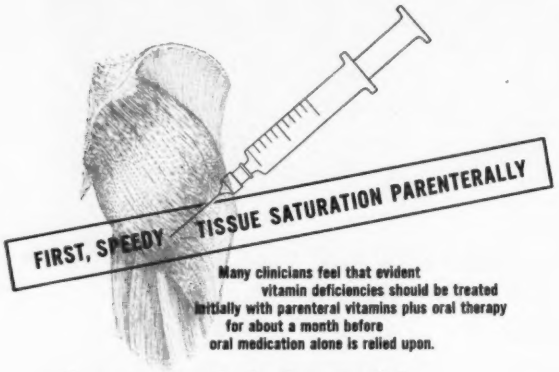
Basis of the method's effectiveness, according to Dr. McLaurin, is the fact that Sulfamylon destroys Pseudomonas, organism considered the cause of most cases of otitis. Sulfamylon is produced by Winthrop-Stearns Inc., New York pharmaceutical firm.

In the method recommended to physicians, Sulfamylon was applied first by Dr. McLaurin, and the patients were shown how to do it themselves. The patient lies on the nonaffected side, instilling a one per cent aqueous solution of the preparation into the infected ear.

The solution is left there for exactly five minutes. Then the ear is blotted dry with cotton, and a cotton wick is inserted. The patient must change the wick often enough to keep it from becoming saturated with discharge. Treatment is carried out twice a day.

Laboratory studies conducted by Dr. McLaurin determined that the 1 per cent solution of Sulfamylon was most effective. It was preferred to other drugs because its pH is acid.

Most of the time the disease is not of fungus origin, Dr. McLaurin stated. Before World War II, it was held that the infection was of low frequency and caused by fungi. Dr. McLaurin noted that there has been "surprising uniformity in recent bacteriological studies, both military and civilian, to the effect that one special organism, Pseudomonas, is the predominant organism, or the only organism present in most cases."



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